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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6:
C07D 237/04, A61K 31/50, C07D 401/04, 211/16, A61K 31/445, C07D 403/06, 401/06, 265/30, A61K 31/535, C07D 275/02

A1

(11) International Publication Number: WO 95/33731

(43) International Publication Date: 14 December 1995 (14.12.95)

(21) International Application Number: PCT/EP95/01956

(22) International Filing Date: 23 May 1995 (23.05.95)

(30) Priority Data:
9411598.7 9 June 1994 (09.06.94) GB

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(81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

Published

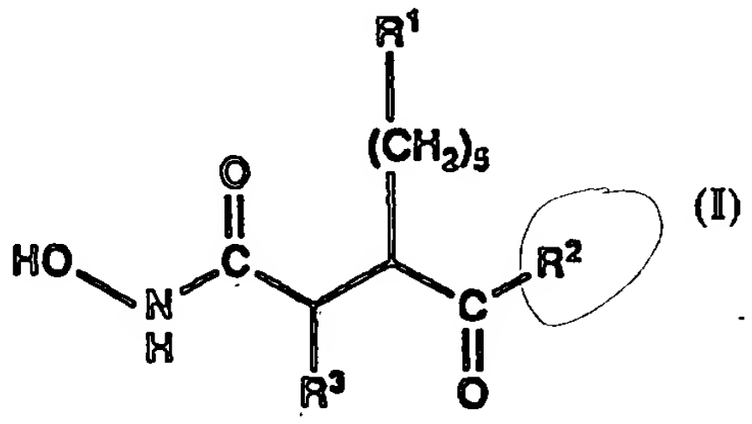
With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: HYDROXAMIC ACID DERIVATIVES

(57) Abstract

The invention provides hydroxamic acid derivatives of general formula (I) wherein R^1 represents 1-7C alkyl; R^2 represents a saturated 5-, 6- or 7-membered monocyclic or bridged N-heterocyclic ring which is attached via the N atom and which, when it is monocyclic, optionally contains $-NR^4-$, -O-, -S-, -SO- or $-SO_2-$ as a ring member and/or is optionally benz-fused or optionally substituted on one or more C atoms by hydroxy, 1-6C alkyl, 1-6C alkoxy, oxo, ketalized oxo, amino, protected amino, mono(1-6C alkyl)amino, di(1-6C alkyl)amino, (1-6C alkoxy)carbonyl, hydroxymethyl, (1-6C alkoxy-methyl, hydroxyimino, carbamoyl, mono(1-6C alkyl)carbamoyl, di(1-6C alkyl)carbamoyl, N-(1-6C alkyl)-N-(1-6C alkoxy)carbamoyl, aryl-(1-6C alkyl-carbamoyl, 3-6C cycloalkylcarbamoyl, 2,2,6,6-tetra(1-6C alkyl)-4-piperidinyl-carbonyl or 1,2,2,6,6-penta(1-6C alkyl)-4-piperidinylcarbonyl; R^3 represents 1-6C alkyl or a group of the formula $-(CH_2)_m$-aryl or $-(CH_2)_m$-Het in which m stands for 1-4 and Het represents a 5- or 6-membered N-heterocyclic ring which (a) is attached via the nitrogen atom, (b) optionally contains N, O and/or S as additional hetero atom(s), (c) is substituted by oxo on one or both C atoms adjacent to the linking N atom and (d) is optionally benz-fused or optionally substituted on one or more other carbon atoms by 1-6C alkyl or oxo and/or on any additional N atom(s) by 1-6C alkyl or aryl; R^4 represents hydrogen, 1-6C-alkyl, aryl or a protecting group; and pharmaceutically acceptable salts thereof, which are matrix metalloproteinase inhibitors useful in the control or prevention of degenerative joint diseases such as rheumatoid arthritis and osteoarthritis or in the treatment of invasive tumours, atherosclerosis or multiple sclerosis.



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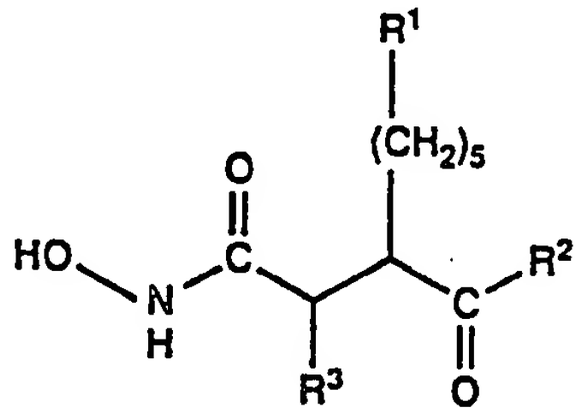
Hydroxamic acid derivatives

The present invention is concerned with hydroxamic acid derivatives.

The hydroxamic acid derivatives provided by the present invention are compounds of the general formula



(I)

wherein

R^1 represents 1-7C alkyl;

R^2 represents a saturated 5-, 6- or 7-membered monocyclic or bridged N-heterocyclic ring which is attached via the N atom and which, when it is monocyclic, optionally contains $-NR^4-$, -O-,-S-, -SO- or $-SO_2-$ as a ring member and/or is optionally benz-fused or optionally substituted on one or more C atoms by hydroxy, 1-6C alkyl, 1-6C alkoxy, oxo, ketalized oxo, amino, protected amino, mono(1-6C alkyl)amino, di(1-6C alkyl)amino, (1-6C alkoxy)carbonyl, hydroxymethyl, (1-6C alkoxy)methyl, hydroxyimino, carbamoyl, mono(1-6C alkyl)carbamoyl, di(1-6C alkyl)carbamoyl, N-(1-6C alkyl)-N-(1-6C alkoxy)carbamoyl, aryl-(1-6C alkyl)carbamoyl, 3-6C cycloalkylcarbamoyl, 2,2,6,6-tetra(1-6C alkyl)-4-piperidinylcarbamoyl or 1,2,2,6,6-penta(1-6C alkyl)-4-piperidinylcarbamoyl;

R^3 represents 1-6C alkyl or a group of the formula $-(CH_2)_m$-aryl or $-(CH_2)_m$-Het in which m stands for 1-4 and Het represents a 5- or 6-membered N-heterocyclic ring which (a) is attached via the nitrogen atom, (b) optionally contains N, O and/or S as additional hetero atom(s), (c) is substituted by oxo on one or both C atoms adjacent to the linking N atom and (d) is optionally benz-fused or optionally substituted on one or more other carbon atoms by 1-6C alkyl or oxo and/or on any additional N atom(s) by 1-6C alkyl or aryl; and

R^4 represents hydrogen, 1-6 alkyl, aryl or a protecting group;
and pharmaceutically acceptable salts thereof.

The compounds of formula I possess valuable pharmacological properties. In particular, they are matrix metalloproteinase inhibitors and can be used in the control or prevention of degenerative joint diseases such as rheumatoid arthritis and osteoarthritis or in the treatment of invasive tumours, atherosclerosis or multiple sclerosis.

Objects of the present invention are the compounds of formula I and their pharmaceutically acceptable salts per se and for use as therapeutically active substances; a process for the manufacture of said compounds and salts; intermediates useful in said process; medicaments containing said compounds and salts and the manufacture of these medicaments; and the use of said compounds and salts in the control or prevention of illnesses or in the improvement of health, especially in the control or prevention of degenerative joint diseases or in the treatment of invasive tumours or atherosclerosis, or for the manufacture of a medicament for the control or prevention of degenerative joint diseases or for the treatment of invasive tumours, atherosclerosis or multiple sclerosis.

The alkyl and alkoxy groups referred to in this Specification contain the specified number of carbon atoms and can be straight-chain or branched-chain. Examples of alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.butyl, tert.butyl and the like and examples of alkoxy groups are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec.butoxy, tert.butoxy, pentyloxy and the like. Methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl and the like are examples of (1-6C alkoxy)carbonyl groups. A ketalized oxo group can be, for example, ethylenedioxy. An aryl group can be phenyl or naphthyl, preferably phenyl, which is optionally substituted, for example by halogen, i.e. fluorine, chlorine, bromine or iodine, 1-6C alkyl, 1-6C alkoxy, trifluoromethyl and the like. The 3-6C cycloalkyl group is cyclopropy, cyclobutyl, cyclopentyl or cyclohexyl.

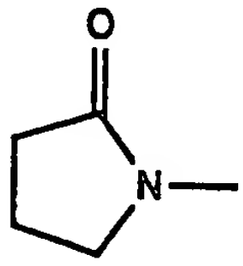
A protecting group denoted by R^4 and the protecting moiety of a protected amino group as a possible substituent on R^2 can be any conventional protecting group, e.g. as known in peptide chemistry such as

benzyloxycarbonyl, tert.butoxycarbonyl, formyl, trifluoroacetyl, 2-(biphenylyl)isopropoxycarbonyl, isobornyloxycarbonyl and the like.

Examples of monocyclic N-heterocyclic rings denoted by R^2 are pyrrolidino, piperidino, morpholino, tetrahydro-1,4-thiazin-4-yl, thiazolidin-3-yl, hexahydro-2-pyridazinyl, hexahydroazepino and the like, which can be benz-fused or substituted in the manner given earlier.

Examples of bridged N-heterocyclic rings denoted by R^2 are 5-azabicyclo[2.1.1]hexane, 3-azabicyclo[3.1.1]heptane, 7-azabicyclo[2.2.1]heptane, 3-azabicyclo[3.2.1]octane, 2-azabicyclo[3.2.2]nonane and 3-azabicyclo[3.2.2]-nonane.

Examples of N-heterocyclic rings denoted by Het in R^3 are rings of the formulae:



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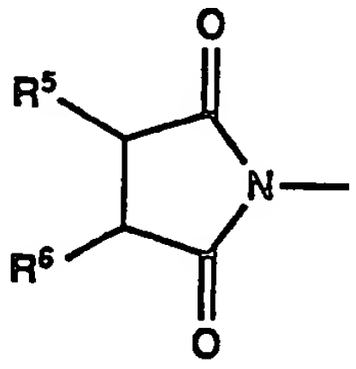

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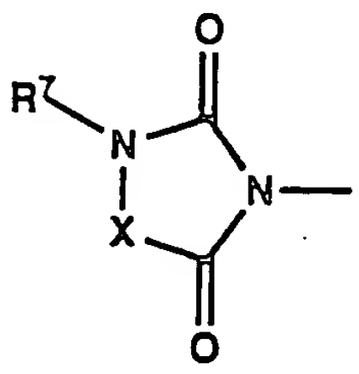

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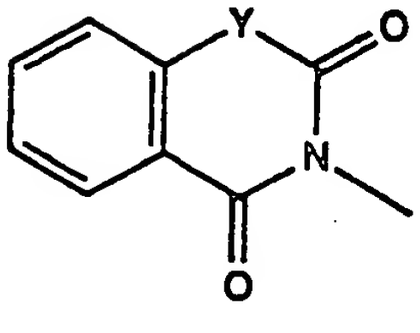

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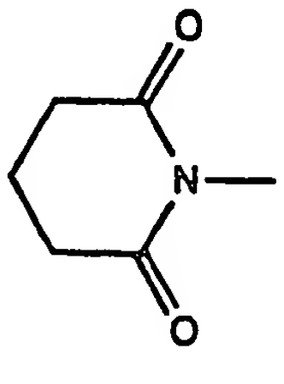

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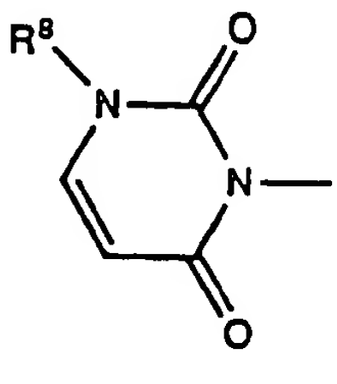
and



(f)

in which

R^5 and R^6 each represent hydrogen or together represent an additional bond or the remainder of a fused benzene ring;

R^7 represents hydrogen, lower alkyl or aryl; and

X represents -CO-, -CH_2-, -CH(lower alkyl)-, -C(lower alkyl)$_2$-, -NH-, -N(lower alkyl)- or -O-; or, when R^7 represents lower alkyl and X represents -N(lower alkyl)-, the lower alkyl groups can be joined to form a 5-, 6- or 7-membered ring;

R^8 represents hydrogen, lower alkyl or aryl; and

Y represents -O-, -NH- or -N(lower alkyl)-.

Examples of such rings are 2-oxo-1-pyrrolidinyl, 2,5-dioxo-1-pyrrolidino, phthalimido, 1,2-dimethyl-3,5-dioxo-1,2,4-triazolidin-4-yl, 3-methyl-2,5-dioxo-1-imidazolidinyl, 3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl, 2-methyl-3,5-dioxo-1,2,4-oxadiaxol-4-yl, 3-methyl-2,4,5-trioxo-1-imidazolidinyl, 2,5-dioxo-3-phenyl-1-imidazolidinyl and 2,6-dioxopiperidino.

Preferred compounds of formula I are those in which R^1 represents ethyl or n-butyl.

R^2 preferably represents a saturated monocyclic N-heterocyclic ring, especially a pyrrolidino, piperidino, morpholino, thiazolidin-3-yl, piperazino or hexahydro-2-pyridazinyl ring and particularly 2-(methylcarbamoyl)-pyrrolidino, 2-(methylcarbamoyl)-4-hydroxy-pyrrolidino, piperidino, 1,2,3,4-tetrahydroisoquinolino, 1,4-dioxa-8-azaspiro[4.5]decan-8-yl, 4-(methyl-carbamoyl)-5,5-dimethyl-thiazolidin-3-yl, 4-(methylcarbamoyl)-5,5-dimethyl-thiazolidin-3-yl S,S-dioxide, 4-(methylcarbamoyl)-thiazolidin-3-yl, 4-(methyl-carbamoyl)-thiazolidin-3-yl S,S-dioxide, 4-phenylpiperazino, hexahydro-2-pyridazinyl or hexahydro-2-pyridazinyl which is substituted in the 3-position by methylcarbamoyl, cyclohexylcarbamoyl, 2,2,6,6-tetramethyl-4-piperidinyl-carbamoyl, 1,2,2,6,6-pentamethyl-4-piperidinylcarbamoyl, N-methyl-N-methoxycarbamoyl, dimethylcarbamoyl or α-methylbenzylcarbamoyl or in the 3-position by α-methylbenzylcarbamoyl and in the 1-position by benzyl-oxycarbonyl.

R^3 preferably represents methyl or a group of the formula -$(CH_2)_m$-aryl or -$(CH_2)_m$-Het. The group of the formula -$(CH_2)_m$-aryl is especially 2-phenylethyl or 3-phenylpropyl and the group of the formula -$(CH_2)_m$-Het is especially a group of formula (c), particularly when R^7 represents lower alkyl and X represents -C(lower alkyl)$_2$-. 3,4,4-Trimethyl-2,5-dioxo-1-imidazolidinyl, i.e. R^7 represents methyl and X represents -$C(CH_3)_2$-, is the most preferred -$(CH_2)_m$-Het group.

Particularly preferred compounds of formula I provided by the present invention are:

2-[2(R)-[1(R or S)-(Hydroxycarbamoyl)-4-phenylbutyl]nonanoyl]-hexahydro-N-methyl-3(S)-pyridazinecarboxamide

N-cyclohexyl-hexahydro-2-[2(R)-[1(RS)-(hydroxycarbamoyl)-4-phenylbutyl]nonanoyl]-3(S)-pyridazinecarboxamide,

hexahydro-2-[2(R)-[1(RS)-(hydroxycarbamoyl)-4-phenylbutyl]-nonanoyl]-N-(2,2,6,6-tetramethyl-4-piperidinyl)-3(S)-pyridazinecarboxamide,

1-[2(R)-[1(R or S)-(hydroxycarbamoyl)-4-phenylbutyl]nonanoyl]-piperidine,

N2-[2R-[1(RS)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]nonanoyl]-N1-methyl-L-prolinamide,

1-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]nonanoyl]piperidine,

hexahydro-2-[2(R)-1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]nonanoyl]-N-methyl-3(S)-pyridazine-carboxamide,

hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)-3-phenylpropyl]-undecanoyl]-N-methyl-3(S)-pyridazinecarboxamide,

hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)-3-phenylpropyl]-undecanoyl]-N-methoxy-N-methyl-3(S)-pyridazinecarboxamide,

hexahydro-2-[2(R or S)-(1(S)-(hydroxycarbamoyl)-3-phenylpropyl]-undecanoyl]-N-(1,2,2,6,6-pentamethyl-4-piperidinyl)-3(S)-pyridazine-carboxamide

hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl]-N-methyl-3(S)-pyridazinecarboxamide,

hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)-3-phenylpropyl]-nonanoyl]-N-methyl-3(S)-pyridazinecarboxamide,

hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]nonanoyl]-N-methyl-3(S)-pyridazinecarboxamide,

1-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl]piperidine,

1-[2-(R or S)-[1(S)-(hydroxycarbamoyl)-3-phenylpropyl]undecan-oyl]piperidine,

hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)-3-phenylpropyl]-undecanoyl]-N-(2,2,6,6-tetramethyl-4-piperidinyl)-3(S)-pyridazine carboxamide,

hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl]-N-(2,2,6,6-tetramethyl-4-piperidinyl)-3(S)-pyridazinecarboxamide,

1-[2(R or S)-[1(S)-(hydroxycarbamoyl)-4-phenylbutyl]undecanoyl]-piperidine,

4-[2(R or S)-[1(S)-(hydroxycarbamoyl)-4-phenylbutyl]undecanoyl]-morpholine and

1-(benzyloxycarbonyl)-hexahydro-2-[2(R)-[1(R or S)-(hydroxy-carbamoyl)-4-phenylbutyl]nonanoyl]-N-(α(S)-methylbenzyl)-3(S)-pyridazine-carboxamide.

Other preferred compounds of formula I are:

Hexahydro-1-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl]-pyridazine,

hexahydro-2-[2(R)-1(R or S)-(hydroxycarbamoyl)-4-phenylbutyl]-nonanoyl]-N-(alpha(S)-methylbenzyl)-3(S)-pyridazinecarboxamide,

N2-[2(R or S)-[1(S)-(hydroxycarbamoyl)-4-phenylbutyl]undecanoyl]-N1-methyl-L-prolinamide,

3-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl-N,5,5-trimethyl-4(R)-thiazolidinecarboxamide,

3-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl-N,5,5-trimethyl-4(R)-thiazolidinecarboxamide S,S-dioxide,

hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl-N-methoxy-N-methyl-3(S)-pyridazinecarboxamide,

hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl-N,N-dimethyl-3(S)-pyridazinecarboxamide,

3-[2(R or S)-[1(S)-(hydroxycarbamoyl)-4-phenylbutyl]undecanoyl]-N-methyl-4(R)-thiazolidinecarboxamide,

3-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]undecanoyl]-N-methyl-4(R)-thiazolidinecarboxamide S,S-dioxide,

hexahydro-2-[2(R)-[1(R or S)-(hydroxycarbamoyl)-4-phenylbutyl]-nonanoyl]-N,N-dimethyl-3(S)-pyridazinecarboxamide,

4-[2(R or S)-[1(S)-(hydroxycarbamoyl)-3-phenylpropyl]undecanoyl]-morpholine,

4-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl]morpholine,

N2-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl]-N1-methyl-L-prolinamide,

4(R)-hydroxy-N2-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl]-N1-methyl-L-prolinamide,

1,2,3,4-tetrahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)-4-phenylbutyl]-undecanoyl]isoquinoline,

4-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]undecanoyl]morpholine,

3-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]undecanoyl]-N-methyl-4(R)-thiazolidinecarboxamide,

4(R)-hydroxy-N2-[2(R)-[1(S)-(hydroxycarbamoyl)-4-phenylbutyl]-undecanoyl]-N1-methyl-2-prolinamide,

1-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]undecanoyl]-4-phenylpiperazine,

8-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]undecanoyl]-1,4-dioxo-8-azaspiro[4.5]decane and

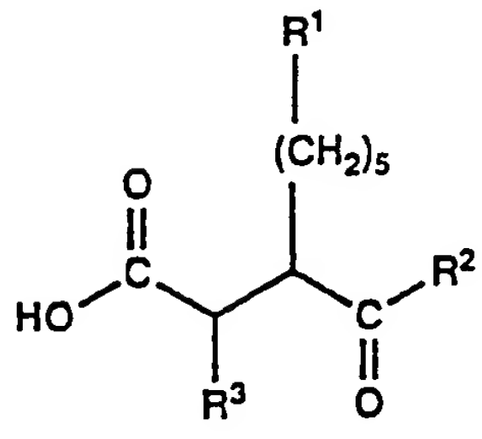
1-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl]-4-phenyl-piperazine.

The compounds of formula I form pharmaceutically acceptable salts with bases such as alkali metal hydroxides (e.g. sodium hydroxide and potassium hydroxide), alkaline earth metal hydroxides (e.g. calcium hydroxide and magnesium hydroxide), ammonium hydroxide and the like. The compounds of formula I which are basic form pharmaceutically acceptable salts with acids. As such salts there come into consideration not only salts with inorganic acids such as hydrohalic acids (e.g. hydrochloric acid and hydrobromic acid), sulphuric acid, nitric acid, phosphoric acid etc, but also salts with organic acids such as acetic acid, tartaric acid, succinic acid, fumaric acid, maleic acid, malic acid, salicylic acid, citric acid, methanesulphonic acid, p-toluenesulphonic acid etc.

The compounds of formula I contain at least two asymmetric carbon atoms and can accordingly exist as optically active enantiomers, as diastereoisomers or as racemates. The present invention is intended to embrace all of these forms.

According to the process provided by the present invention, the compounds of formula I and their pharmaceutically acceptable salts are manufactured by

(a) reacting an acid of the general formula



(II)

wherein R^1, R^2 and R^3 have the significance given earlier, with a compound of the general formula

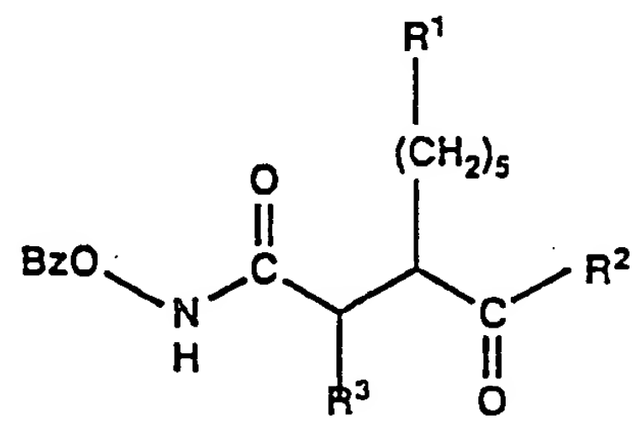
$H_2N\text{-}OZ$ (III)

wherein Z represents hydrogen, tri(lower alkyl)silyl or diphenyl(lower alkyl)silyl,

and, where required, cleaving off any diphenyl(lower alkyl)silyl group present in the reaction product,

or

(b) catalytically hydrogenating a compound of the general formula



(IV)

wherein R^1, R^2 and R^3 have the significance given earlier and Bz represents benzyl,

and,

if desired, converting a compound of formula I obtained into a pharmaceutically acceptable salt.

The reaction of an acid of formula II with a compound of formula III in accordance with embodiment (a) of the process can be carried out in a known manner. For example, an acid of formula II can be reacted with a

compound of formula III in an inert organic solvent such as dichloromethane, dimethylformamide or the like using 1-hydroxybenzotriazole in the presence of a condensation agent such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride at about 0°C to about room temperature. Alternatively, an acid of formula II can be converted into the corresponding acid chloride (e.g. using oxalyl chloride) and the acid chloride can then be reacted with a compound of formula III. Preferred compounds of formula III are those in which Z represents tert.butyl-dimethylsilyl or tert.butyl-diphenylsilyl. When a compound of formula III in which Z represents tri(lower alkyl)silyl is used, this group is cleaved off during the reaction and working-up, and a compound of formula I is obtained directly. On the other hand, when a compound of formula III in which Z represents diphenyl-(lower alkyl)silyl is used, this group remains in the reaction product and must subsequently be cleaved off in a known manner, for example by means of fluoride ions.

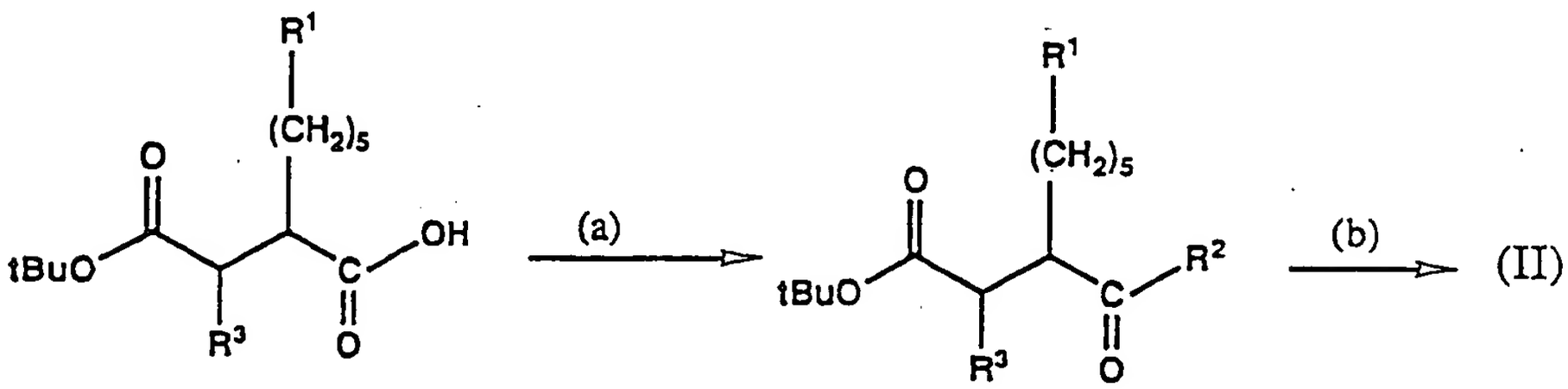
The catalytic hydrogenation of a compound of formula IV in accordance with embodiment (b) of the process can be carried out in a manner known per se; for example in an inert organic solvent using hydrogen in the presence of a noble metal catalyst. Suitable inert organic solvents are, for example, lower alkanols such as methanol, ethanol, etc. With respect to the catalyst, this can be, for example, a platinum, palladium or rhodium catalyst which can be supported on a suitable carrier material. Palladium-on-charcoal is the preferred catalyst. The temperature and pressure are not critical, although for convenience the catalytic hydrogenation is preferably carried out at room temperature and under atmospheric pressure.

Compounds of formula I can be converted into pharmaceutically acceptable salts by treatment with bases and basic compounds of formula I can be converted into pharmaceutically acceptable salts by treatment with acids. Such treatments can be carried out in a conventional manner.

The acids of formula II which are used as starting materials in embodiment (a) of the process are novel and form a further object of the present invention.

The acids of formula II can be prepared, for example, as illustrated in Reaction Scheme 1 hereinafter in which R^1, R^2 and R^3 have the significance given earlier and tBu represents tert-butyl:

Reaction Scheme 1



(V) (VI)

In step (a) of this Reaction Scheme a compound of formula V, which is a known compound or an analogue of a known compound, is converted into a compound of formula VI by introduction of the group R^2. This can be carried out in a known manner by condensing the compound of formula V with an amine of the formula HR^2 using a conventional peptide coupling reagent such as 1-hydroxybenzotriazole in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride or by converting the compound of formula V with oxalyl chloride into the corresponding acid chloride and condensing the latter with the amine of the formula HR^2.

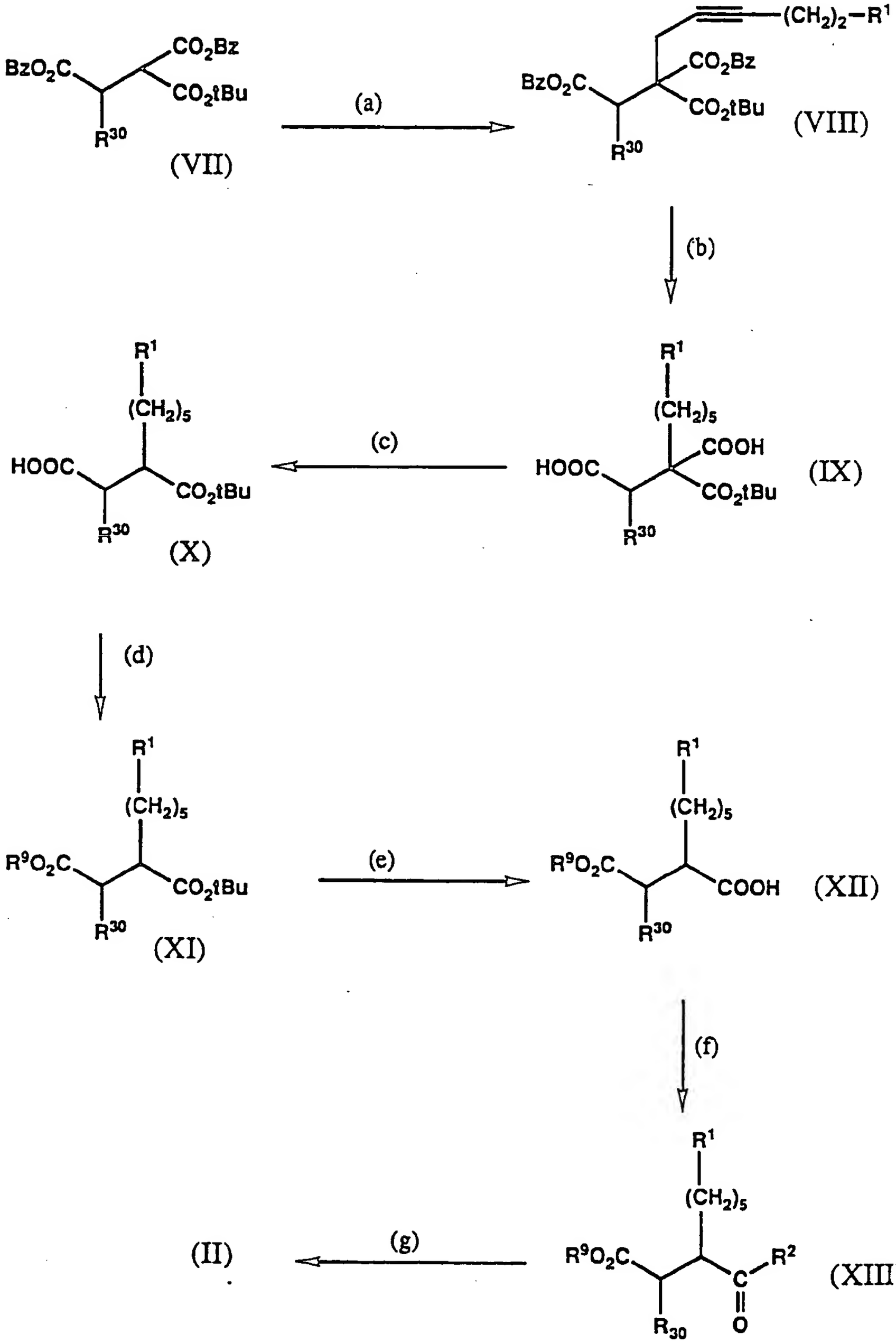
Compounds of formula VI which carry a carbamoyl or substituted-carbamoyl group as hereinbefore defined can also be prepared by condensing a compound of formula V with a carboxy-substituted amine corresponding to HR^2 and subsequently appropriately amidating the condensation product. In a variant of this procedure a corresponding allyloxycarbonyl-substituted amine may be used and in this case the allyl ester obtained as the condensation product is deprotected in a known manner, e.g. by treatment with a palladium(O) compound such as tetrakis(triphenylphosphine)-palladium(O), and then amidated.

In step (b) of Reaction Scheme 1 a compound of formula VI is deprotected to give an acid of formula II. This deprotection is carried out in

a known manner using trifluoroacetic acid, trimethylsilyl bromide or the like.

Acids of formula II in which R^3 represents 1-6C alkyl or a group of the formula $-(CH_2)_m$-aryl can also be prepared as illustrated in Reaction Scheme 2 hereinafter in which R^1, R^2, Bz and tBu have the significance given earlier, R^9 represents allyl or benzyl and R^{30} represents 1-6C alkyl or a group of the formula $-(CH_2)_m$-aryl:

Reaction Scheme 2



Having regard to Reaction Scheme 2, all steps of which can be carried out in a conventional manner, a compound of formula (VII), which is a known compound or an analogue of a known compound, is condensed in step (a) with a bromoalkyne of the formula $Br\text{-}CH_2\text{-}C{\equiv}C\text{-}(CH_2)_2\text{-}R^1$ in the presence of a strong base such as sodium hydride in an inert organic solvent such as dimethylformamide to give a compound of formula VIII. This is then catalytically hydrogenated in step (b), e.g. in the presence of a palladium catalyst, and the resulting compound of formula IX is decarboxylated in step (c), e.g. by heating with a tertiary amine, e.g. triethylamine or N-methylmorpholine in toluene, to give a compound of formula X. The latter is protected at the carboxy group in step (d) by reaction with benzyl bromide or, where an acid of formula II in which R^2 contains a benzyloxycarbonyl-protected nitrogen atom is to be prepared, by reaction with allyl bromide. Deprotection of the resulting compound of formula XI at the tert.butoxycarbonyl group in step (e) using trifluoroacetic acid yields a compound of formula XII which in step (f) is condensed with an amine of the formula HR^2 in an analogous manner to that described in step (a) of Reaction Scheme 1 to give a compound of formula XIII. Finally, the group R^9 is removed from a compound of formula XIII in step (g) by catalytic hydrogenation when R^9 represents benzyl or by treatment with a palladium(O) compound when R^9 represents allyl to give the desired acid of formula II.

The compounds of formula IV which are used as starting materials in embodiment (b) of the process are novel and form a further object of the present invention.

The compounds of formula IV can be prepared, for example, by reacting an acid of formula II with O-benzylhydroxylamine. This reaction can be carried out in a known manner, for example in an inert organic solvent such as dichloromethane or dimethylformamide using 1-hydroxy-benzotriazole in the presence of a condensation agent such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride. If desired, a compound of formula IV in which R^2 is substituted by tert.butoxycarbonyl can be converted into a corresponding compound of formula IV in which R^2 is substituted by carbamoyl or substituted-carbamoyl as hereinbefore defined by deprotection at the tert.butoxycarbonyl group using trifluoroacetic acid and subsequent amidation.

The remaining compounds which are used as intermediates or reactants in the manufacture of the compounds of formula I are known compounds or analogues of known compounds which can be prepared in a similar manner to the known compounds.

As mentioned earlier, the compounds of formula I and their pharmaceutically acceptable salts are matrix metalloproteinase inhibitors. These activities can be demonstrated using the test procedures described hereinafter:

Collagenase (Test A)

This test demonstrates the in vitro collagenase inhibiting activity and is carried out using collagenase obtained from a culture of human synovial fibroblasts according to the method of Dayer J-M et al., Proc. Natl. Acad. Sci. USA (1976), 73 945, following activation of the pro-collagenase in the conditioned medium by treatment with trypsin. Collagenase activity was measured using ^{14}C-acetylated collagen type I from rat tail tendons as the substrate and employing the microtitre plate assay method of Johnson-Wint, B, Anal. Biochem. (1980), 104, 175. The IC_{50} is that concentration of a test compound in the enzyme digestion which reduces substrate cleavage and solubilization to 50% of that achieved by the enzyme alone.

Stromelysin (Test B)

Prostromelysin was purified from human fibroblast culture medium by prostromelysin antibody affinity chromatography [Ganja-Smith Z, Nagase H, Woessner J F Jr., Biochem J. 1989, vol 285 (1), pp 115-119]. The latent pro-enzyme was activated by incubation with trypsin (5 µg/ml) at 25°C for 2 hours and after this time the trypsin was inactivated using a ten-fold excess of soya bean trypsin inhibitor. The inhibitory activity of the aforementioned hydroxamic acid derivatives was determined using ^{14}C-acetylated b-casein substrate. The stromelysin (20 nM) was added to a solution of substrate (4 mg/ml) and varying concentrations of test compound in 50 mM Tris HCl buffer, pH 7.5, containing 10 mM $CaCl_2$ and 0.05% Brij®. The solution obtained was incubated at 37°C for 20 hours. Enzyme digestion of the substrate was terminated by the addition of trichloroacetic acid to a final

concentration of 7.5% and the precipitated undigested substrate was pelleted by centrifugation at 10000 g for 0.25 hour. The supernatant was aspired and ^{14}C activity was determined by liquid scintillation spectrometry. The IC_{50} is that concentration of test compound in the enzyme digestion which reduces the substrate cleavage to 50% of that achieved by the enzyme alone.

Stromelysin (Test C)

The latent pro-enzyme was activated by incubation with trypsin (1 μg/ml) for 30 minutes at 25°C and then the trypsin was inactivated using a thirty-fold excess of trypsin inhibitor. The inhibitory activity of the hydroxamic acid derivatives was determined using the fluorescent peptide substrate (7-methoxycoumarin-4-yl)acetyl-L-prolyl-L-leucyl-L-alanyl-L-nonalyl-[3-(2,4-dinitrophenyl)-L-2,3-diaminopropyl]-L-arginyl-L-arginine. The stromelysin (approximate concentration of 200 pM) was added to a solution of substrate (4 μM) and varying concentrations of test compound in 50mM Tris HCl buffer, pH 7.5 containing 10mM $CaCl_2$ and 0.05% Brij® 35. This solution was incubated for 16 hours at 37°C, following which the action of stromelysin was stopped by the addition of an acetic acid solution. Product formation was determined by spectrofluorometry using an excitation wavelength of 325 nm and an emission wavelength of 395 nm. The IC_{50} is that concentration of test compound which reduces the substrate cleavage to 50% of that achieved by the enzyme alone.

Gelatinase (Test D)

In this test, which demonstrates the in vitro inhibitory activity against gelatinase B obtained from human neutrophils, pro-gelatinase B was purified from human neutrophils by firstly separating the neutrophils from human blood by density centrifugation and dextran sedimentation. The separated neutrophils were disrupted by combined treatment with 0.05% Triton X-100® and sonification. Cell debris was then removed by high speed centrifugation. Pro-gelatinase B was purified from the supernatant by gelatine agarose affinity chromatography, the bound pro-enzyme being eluted from the affinity matrix by a 10% dimethyl sulphoxide/buffer wash. Analysis of the purified material revealed a single protein band with a molecular weight of 95 kDa when visualized by SDS-PAGE. The gelatinase B was activated by incubation in the presence of 150 μM trypsin for 1 hour at 37°C and the action of the

trypsin was then inhibited by the addition of a ten-fold excess of trypsin inhibitor. The inhibitory activity of the test compounds was determined using the synthetic substrate N-[(7-methoxy-2-oxo-2H-benzopyran-4-yl)acetyl]-L-prolyl-L-leucine-glycyl-L-leucyl-L-[3-(2,4-dinitroanilino-L-alanyl]-L-alanyl-L-arginamide trifluoroacetate (1:1). The gelatinase (approximately 200 pM) was added to a solution of 2 μM substrate in 50 mM borate buffer (pH 7.5) containing 1 mM $CaCl_2$ and 0.05% Brij 35® and a known amount of test compound. The solution obtained was incubated at 37°C for 4 hours. Product formation was determined spectrofluorometrically using an excitation wavelength of 325 nm and an emission wavelength of 395 nm. The IC_{50} is that concentration of test compound which reduces the product formed to 50% of that achieved by enzyme alone.

The results obtained in the foregoing tests using, as test compounds, representative hydroxamic acid derivatives provided by this invention are compiled in the following Table:

Table

Compound of Example No.	Test A IC_{50} (mol)	Test B IC_{50} (mol)	Test C IC_{50} (mol)	TestD IC_{50} (mol)
3			5.7×10^{-10}	2.3×10^{-10}
7	5.6×10^{-9}		1.0×10^{-8}	7.8×10^{-10}
9		6.1×10^{-8}	3.1×10^{-8}	1.97×10^{-9}
4		8.4×10^{-7}		2.23×10^{-8}

The compounds of formula I and their pharmaceutically acceptable salts can be used as medicaments, for example in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. However, they can also be administered rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

For the manufacture of pharmaceutical preparations the compounds of formula I and their pharmaceutically acceptable salts can be formulated with therapeutically inert, inorganic or organic carriers. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used, for example, as

such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active ingredient no carriers are, however, generally required in the case of soft gelatine capsules. Suitable carriers for the manufacture of solutions and syrups are, for example, water, polyols, saccharose, invert sugar, glucose and the like. Suitable carriers for the manufacture of injection solutions are, for example, water, alcohols, polyols, glycerine, vegetable oils and the like. Natural and hardened oils, waxes, fats, semi-liquid polyols and the like are suitable carriers for the manufacture of suppositories.

The pharmaceutical preparations can also contain preservatives, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for adjustment of the osmotic pressure buffers coating agents or antioxidants.

Medicaments containing a compound of formula I or a pharmaceutically acceptable salt thereof and a therapeutically acceptable carrier as well as a process for the manufacture of such medicaments are also objects of the present invention. This process comprises mixing a compound of formula I or a pharmaceutically acceptable salt thereof with a therapeutically inert carrier material and bringing the mixture into a galenical administration form.

As mentioned earlier, the compounds of formula I and their pharmaceutically acceptable salts can be used in the control or prevention of illnesses, especially in the control or prevention of degenerative joint diseases or in the treatment of invasive tumours, atherosclerosis or multiple sclerosis. The dosage can vary within wide limits and will, of course, be adjusted to the individual requirements in each particular case. In general, in the case of administration to adults, a daily dosage of from about 5 mg to about 30 mg, preferably from about 10 mg to about 15 mg, should be appropriate, although the upper limit may be exceeded when this is found to be expedient. The daily dosage can be administered as a single dosage or in divided dosages.

The following Examples illustrate the present invention in more detail. In these Examples all temperatures are given in degrees Celsius.

Example 1

0.2 g of benzyl hexahydro-2-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-4-phenylbutyl]nonanoyl]-3(S)-(methylcarbamoyl)-1-pyridazinecarboxylate (diastereoisomer 1) in 15 ml of methanol was hydrogenated in the presence of 0.06 g of 10% palladium on carbon for 1 hour. The catalyst was filtered off and the solvent evaporated. The residue was triturated with hexane and filtered to give 0.1 g of 2-[2(R)-[1(R or S)-(hydroxycarbamoyl)-4-phenylbutyl]-nonanoyl]-hexahydro-N-methyl-3(S)-pyridazinecarboxamide (diastereoisomer 1) in the form of a white solid;
nmr (MeOD); 7.17-7.00 (m,5H); 4.95 (m,1H); 3.91-3.76 (m,1H); 2.93-2.85 (m,1H); 2.64 (s,3H); 2.56-2.45 (m,3H); 2.19-2.07 (m,1H); 1.95-1.88 (m,1H); 1.65-1.04 (m,19H); 0.79 (t,3H,J=6);
MS: 475 $(M+H)^+$.

The starting material was prepared as follows:

(i) A solution of 0.38 g of 4-tert.butyl 2(R)-heptyl-3(R or S)-(3-phenyl-propyl)succinate in 20 ml of dry toluene was cooled to -10°C. Four drops of N,N-dimethylformamide were added, followed by 0.1 ml of oxalyl chloride. The mixture was stirred at -10°C for 1 hour and then a solution of 0.685 g of hexahydro-1-(benzyloxycarbonyl)-3(S)-pyridazinecarboxylic acid and 1.77 g of triethylamine in 20 ml of dichloromethane was added over 1 minute. The mixture was gradually allowed to return to ambient temperature and was stirred for a total of 3.5 hours. The solvent was evaporated and the residue was dissolved in 50 ml of ethyl acetate and washed successively with 5% citric acid solution, water and saturated brine. The organic layer was dried over anhydrous magnesium sulphate and evaporated to give a colourless gum. The product was purified by flash chromatography on silica gel using hexane/ethyl acetate (2:1) for the elution. 0.66 g of hexahydro-1-(benzyloxy-carbonyl)-2-[2(R)-[1(R or S)-(tert.butoxycarbonyl)-4-phenylbutyl]nonanoyl]-3(S)-pyridazinecarboxylic acid was obtained in the form of a colourless gum.

(ii) A solution of 0.323 g of hexahydro-1-(benzyloxycarbonyl)-2-[2(R)-[1(R or S)-(tert.butoxycarbonyl)-4-phenylbutyl]nonanoyl]-3(S)-pyridazinecarboxylic acid in 5 ml of N,N-dimethylformamide was cooled to 0°C and 0.15 g of 1-hydroxybenzotriazole and 0.18 g of 1-ethyl-3-(3-dimethylaminopropyl)carbodi-imide hydrochloride were added. After 30 minutes 0.3 ml of a 40% aqueous

solution of methylamine was added and the mixture was stirred at ambient temperature for 18 hours. The solvent was evaporated and the residue was treated with 20 ml of 5% aqueous sodium hydrogen carbonate solution. The product was extracted with ethyl acetate and the extract was washed with 5% citric acid and aqueous sodium chloride solution. After drying over anhydrous magnesium sulphate the solvent was evaporated to give a colourless gum which was purified by flash chromatography using ethyl acetate/ hexane (1:2) for the elution. There was obtained 0.235 g of benzyl hexahydro-2-[2(R)-[1(R or S)-(tert.butoxycarbonyl)-4-phenylbutyl]nonanoyl]-3(S)-(methylcarbamoyl)-1-pyridazinecarboxylate in the form of a colourless gum.

(iii) A solution of 0.235 g of benzyl hexahydro-2-[2(R)-[1(R or S)-(tert.butoxycarbonyl)-4-phenylbutyl]nonanoyl]-3(S)-(methylcarbamoyl)-1-pyridazinecarboxylate in 20 ml of dichloromethane was treated with 3.0 ml of trifluoroacetic acid. The mixture was stirred at ambient temperature for 3 hours. The solvent was evaporated and the residue was evaporated three times from toluene. The residue was dissolved in 5 ml of dry N,N-dimethylformamide, cooled to 0°C and stirred under nitrogen during successive additions of 0.08 g of 1-hydroxybenzotriazole, 0.06 ml of N-methylmorpholine, 0.07 g of O-benzylhydroxylamine and 0.11 g of 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride. The mixture was allowed to return to ambient temperature and was stirred overnight. The solvent was evaporated and the residue was treated with 5% aqueous sodium hydrogen carbonate solution. The product was extracted with ethyl acetate and the ethyl acetate extract was washed with dilute hydrochloric acid and saturated brine. After drying over anhydrous magnesium sulphate the solvent was evaporated and the residue was purified by flash chromatography on silica gel using ethyl acetate/ hexane (1:1) for the elution. There was obtained 0.202 g of benzyl hexahydro-2-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-4-phenylbutyl]nonanoyl]-3(S)-(methylcarbamoyl)-1-pyridazinecarboxylate (diastereoisomer 1) in the form of a colourless gum.

Example 2

In a manner analogous to that described in the first paragraph of Example 1, from 0.33 g of benzyl hexahydro-2-[2(R)-[1(RS)-(benzyloxycarbamoyl)-4-phenylbutyl]nonanoyl]-3(S)-(cyclohexylcarbamoyl)-1-

pyridazinecarboxylate (6:1 mixture of diastereoisomers) there was obtained 0.174 g of N-cyclohexyl-hexahydro-2-[2(R)-[1(RS)-(hydroxycarbamoyl)-4-phenylbutyl]nonanoyl]-3(S)-pyridazinecarboxamide (6:1 mixture of diastereoisomers) in the form of a white solid.
nmr (MeOD): 7.26-7.09 (m,5H); 5.03 (m,1H); 4.02-3.86 (m,1H); 3.68-3.59 (m,1H); 3.03-2.95 (m,1H); 2.66-2.53 (m,3H); 2.28-2.16 (m,1H); 2.05-1.97 (m,1H); 1.91-1.12 (m,29H); 0.89 (t,3H,J=6);
MS: 543 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 1(ii) and (iii) from 0.38 g of hexahydro-1-(benzyloxycarbonyl)-2-[2(R)-[1(RS)-(tert.-butoxycarbonyl)-4-phenylbutyl]nonanoyl]-3(S)-pyridazinecarboxylic acid and 0.1 g of cyclohexylamine there was obtained 0.338 g of benzyl hexahydro-2-[2(R)-[1(RS)-(benzyloxycarbamoyl)-4-phenylbutyl]nonanoyl]-3(S)-(cyclohexyl-carbamoyl)-1-pyridazinecarboxylate in the form of a colourless gum;
MS: 767 $(M+H)^+$.

Example 3

In a manner analogous to that described in the first paragraph of Example 1, from 0.33 g of 2-[2(R)-[1(RS)-(benzyloxycarbamoyl)-4-phenyl-butyl]nonanoyl]-1-(benzyloxycarbonyl)-hexahydro-N-(2,2,6,6-tetramethyl-4-piperidinyl)-3(S)-pyridazinecarboxamide (6:1 mixture of diastereoisomers) there was obtained 0.068 g of hexahydro-2-[2(R)-[1(RS)-(hydroxycarbamoyl)-4-phenylbutyl]nonanoyl]-N-(2,2,6,6-tetramethyl-4-piperidinyl)-3(S)-pyridazine-carboxamide (7:1 mixture of diastereoisomers) in the form of a white solid.
nmr (MeOD): 7.25-7.09 (m,5H); 5.02 (m,1H); 4.34-4.23 (m,1H); 4.00-3.86 (m,1H); 3.03-2.95 (m,1H); 2.67-2.52 (m,3H); 2.29-2.15 (m,1H); 2.08-1.97 (m,3H); 1.80-1.11 (m,33H); 0.87 (t,3H,J=6);
MS 600 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 1(ii) and (iii), from 0.39 g of hexahydro-1-(benzyloxycarbonyl)-2-[2(R)-[1(RS)-(tert.-butoxycarbonyl)-4-phenylbutyl]nonanoyl]-3(S)-pyridazinecarboxylic acid and

0.13 g of 4-amino-2,2,6,6-tetramethylpiperidine there was obtained 0.332 g of 2-[2(R)-[1(RS)-(benzyloxycarbamoyl)-4-phenylbutyl]nonanoyl]-1-(benzyloxycarbonyl)-hexahydro-N-(2,2,6,6-tetramethyl-4-piperidinyl)-3(S)-pyridazinecarboxamide (6:1 mixture of diastereoisomers) in the form of a colourless gum.
MS: 824 $(M+H)^+$.

Example 4

In a manner analogous to that described in the first paragraph of Example 1, from 0.24 g of 1-[2(R))-[1(R or S)-(benzyloxycarbamoyl)-4-phenylbutyl]nonanoyl]piperidine there was obtained 0.125 g of 1-[2(R)-[1(R or S)-(hydroxycarbamoyl)-4-phenylbutyl]nonanoyl]piperidine in the form of a white solid.
nmr (MeOD): 7.24-7.06 (m,5H); 3.71-3.62 (m,2H); 3.56-3.47 (m,1H); 3.45-3.37 (m,1H); 3.12-3.03 (m,1H); 2.55 (t,2H,J=7); 2.30-2.21 (m,1H); 1.75-1.06 (m,22H); 0.86 (t,3H,J=6);
MS: 417 $(M+H)^+$.

The starting material was prepared as follows:

(i) A solution of 0.27 g of an approximately 7:1 mixture of diastereoisomer 1 and diastereoisomer 2 of 4-tert.butyl 2(R)-heptyl-3(RS)-(3-phenylpropyl)-succinate in 4 ml of dry N,N-dimethylformamide was cooled to 0°C while stirring under nitrogen and was treated successively with 0.09 g of piperidine, 0.18 g of 1-hydroxybenzotriazole, 0.18 ml of N-methylmorpholine and 0.23 g of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride. The mixture was left to warm to ambient temperature and was stirred overnight. The solvent was evaporated and the residue was treated with 20 ml of 5% aqueous sodium hydrogen carbonate solution. The product was extracted with three portions of ethyl acetate and the combined extracts were washed with 5% citric acid and saturated aqueous sodium chloride solution. After drying over anhydrous magnesium sulphate the solvent was evaporated to give a colourless gum which was purified by flash chromatography on silica gel using hexane/ethyl acetate (3:1) for the elution. There was obtained 0.272 g of 1-[2(R)-[1(R or S)-(tert.butoxycarbonyl)-4-phenylbutyl]nonanoyl]piperidine in the form of a colourless gum.

(ii) In a manner analogous to that described in Example 1(iii), from 0.27 g of 1-[2(R)-[1(R or S)-(tert.butoxycarbonyl)-4-phenylbutyl]nonanoyl]piperidine there was obtained 0.24 g of 1-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-4-phenylbutyl]nonanoyl]piperidine in the form of a colourless gum.

Example 5

In a manner analogous to that described in the first paragraph of Example 1, from 0.36 g of N2-[2(R)-[1(RS)-(benzyloxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]nonanoyl]-N1-methyl-L-prolinamide (9:1 mixture of diastereoisomers) there was obtained 0.24 g of N2-[2(R)-[1(RS)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]nonanoyl]-N1-methyl-L-prolinamide (9:1 mixture of diastereoisomers) in the form of a white solid.
nmr (MeOD): 4.54-4.27 (m,1H); 3.86-3.75 (m,1H); 3.70-3.45 (m,3H); 3.04-2.79 (m,5H); 2.70 (s,3H); 2.24-1.85 (m,4H); 1.58-1.17 (m,18H); 0.91-0.83 (m,3H);
MS: 496 $(M+H)^+$.

The starting material was prepared as followed:

(i) 6.0 g of dibenzyl 3(RS)-(tert.butoxycarbonyl)-2(R)-heptylsuccinate in 40 ml of dry N,N-dimethylformamide was cooled to 0°C and 0.522 g of 60% sodium hydride dispersion was added. The mixture was stirred at 0°C for 30 minutes and for a further 1.5 hours at ambient temperature. The mixture was cooled to 0°C and 2.86 g of 3-bromomethyl-1,5,5-trimethylhydantoin were added. The mixture was left to come to ambient temperature and was stirred for a further 4 hours. The solvent was evaporated and the residue was partitioned between 20 ml of ethyl acetate and 20 ml of 5% citric acid. The ethyl acetate layer was separated, washed with 20 ml of water and then with 20 ml of saturated sodium chloride solution and dried over magnesium sulphate. The solvent was evaporated and the residue was purified by flash chromatography on silica gel using hexane/ether (2:1) for the elution. There were obtained 6.19 g of dibenzyl 3(RS)-(tert.butoxycarbonyl)-2(R)-heptyl-3-[(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)methyl]succinate in the form of a colourless oil.

(ii) 6.19 g of dibenzyl 3(RS)-(tert.butoxycarbonyl)-2(R)-heptyl-3-[(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)methyl]succinate in 60 ml of ethanol

was hydrogenated in the presence of 0.65 g of 10% palladium on carbon for 24 hours. The catalyst was filtered off and the solvent was evaporated. The residue was dissolved in 50 ml of toluene, 1.05 ml of N-methylmorpholine were added and the mixture was heated under reflux for 1 hour. The solution was cooled and washed in succession with 5% citric acid solution, water and saturated sodium chloride solution and then dried over magnesium sulphate solution. The solvent was evaporated to give 3.90 g of 4-tert.butyl hydrogen 2(R)-heptyl-3(RS)-[(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)methyl]succinate in the form of a pale yellow oil.

(iii) In a manner analogous to that described in Example 4(i) and (ii), from 0.41 g of 4-tert.butyl hydrogen 2(R)-heptyl-3(RS)-[(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)methyl]succinate and 0.13 g of S-prolinemethylamide there was obtained 0.369 g of N2-[2(R)-[1(RS)-(benzyloxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]nonanoyl]-N1-methyl-L-prolinamide as a 9:1 mixture of diastereoisomer 1 and diastereoisomer 2 in the form of a white foam.

Example 6

In a manner analogous to that described in the first paragraph of Example 1, from 0.28 g of 1-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]nonanoyl]piperidine there was obtained 0.165 g of 1-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]nonanoyl]piperidine in the form of a white solid.

nmr (MeOD): 3.79-3.52 (m,4H); 3.43-3.33 (m,2H); 3.24-3.15 (m,1H); 2.96-2.89 (m,1H); 2.84 (s,3H); 1.60-1.11 (m,24H); 0.86 (t,3H,J=6);

MS: 453 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 4(i) and (ii), from 0.41 g of 4-tert.butyl hydrogen 2(R)-heptyl-3(RS)-[(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)methyl]succinate and 0.1 g of piperidine there was obtained 0.28 g of 1-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]nonanoyl]piperidine in the form of a colourless gum.

Example 7

In a manner analogous to that described in the first paragraph of Example 1, from 0.25 g of benzyl hexahydro-2-[2(R)-[1(R or S)-(benzyl-oxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]nonanoyl]-3(S)-(methylcarbamoyl)-1-pyridazinecarboxylate there was obtained 0.122 g of hexahydro-2-[2(R)-1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]nonanoyl]-N-methyl-3(S)-pyridazinecarboxamide in the form of a white solid.
nmr (MeOD): 5.06 (m,1H); 4.00-3.82 (m,1H); 3.75 (dd,1H,J=13.5,8); 3.43 (dd,1H,J=13.5,5); 3.06-2.99 (m,1H); 2.94-2.79 (m,4H); 2.73 (s,3H); 2.08-1.93 (m,2H); 1.69-1.12 (m,21H); 0.87 (t,3H,J=6);
MS:511 $(M+H)^+$.

The starting material was prepared as follows:

(i) A solution of 1.05 g of hexahydro-1-(benzyloxycarbonyl)-(3(S)-pyridazinecarboxylic acid in 16 ml of dry N,N-dimethylformamide was treated with 0.52 g of allyl bromide and 0.3 g of anhydrous potassium carbonate. The mixture was heated at 40°C while stirring under a nitrogen atmosphere for 4 hours. The mixture was cooled to ambient temperature and the solvent was evaporated. The residue was partitioned between 50 ml of ethyl acetate and 50 ml of water. The ethyl acetate layer was separated and washed with 50 ml of saturated sodium chloride solution, dried over anhydrous magnesium sulphate and evaporated. The residue was purified by flash chromatography on silica gel using hexane/ethyl acetate (3:1) for the elution. There were obtained 1.1 g of allyl hexahydro-1-(benzyloxycarbonyl)-(3S)-pyridazinecarboxylate in the form of a colourless oil.

(ii) In a manner analogous to that described in Example 1(i), from 1.37 g of 4-tert.butyl hydrogen 2(R)-heptyl-3(RS)-[(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)methyl]succinate and 1.1 g of allyl hexahydro-1-(benzyloxy-carbonyl)-3(S)-pyridazinecarboxylate there was obtained 0.866 g of hexahydro-1-(benzyloxycarbonyl)-2-[2(R)-[1(R or S)-(tert.butoxycarbonyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]nonanoyl]-3(S)-pyridazinecarboxylic acid allyl ester in the form of a colourless gum.

(iii) A solution of 0.86 g of hexahydro-1-(benzyloxycarbonyl)-2-[2(R)-[1(R or S)-(tert.butoxycarbonyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-nonanoyl]-3(S)-pyridazinecarboxylic acid allyl ester in 10 ml of dry tetrahydrofuran was stirred under an argon atmosphere at ambient temperature and 0.1 g of tetrakis(triphenylphosphine)palladium(O) was added followed by the dropwise addition of 1.0 g of morpholine in 4 ml of dry tetrahydrofuran. After stirring for 45 minutes at ambient temperature the solvent was evaporated and the residue was dissolved in ethyl acetate and washed in succession with 5% aqueous citric acid solution, water and saturated sodium chloride solution. The ethyl acetate solution was dried over anhydrous magnesium sulphate and evaporated to give a yellow oil. After purification by flash chromatography on silica gel using ethyl acetate/hexane (1:1) for the elution there was obtained 0.61 g of hexahydro-1-(benzyloxycarbonyl)-2-[2(R)-[1(R or S)-(tert.butoxycarbonyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]nonanoyl]-3(S)-pyridazinecarboxylic acid in the form of a pale yellow gum.

(iv) In a manner analogous to that described in Example 1(ii) and (iii), from 0.61 g of hexahydro-1-(benzyloxycarbonyl)-2-[2(R)-[1(R or S)-(tert.-butoxycarbonyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-nonanoyl]-3(S)-pyridazinecarboxylic acid there was obtained 0.508 g of benzyl hexahydro-2-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]nonanoyl]-3(S)-(methylcarbamoyl)-1-pyridazinecarboxylate in the form of a colourless gum.

Example 8

In a manner analogous to that described in the first paragraph of Example 1, from 0.245 g of benzyl hexahydro-2-[2(R or S)-[1(S)-(benzyl-oxycarbamoyl)-3-phenylpropyl]undecanoyl]-3(S)-(methylcarbamoyl)-1-pyridazinecarboxylate there was obtained, after purification by flash chromatography on silica gel using dichloromethane/methanol (25:1) for the elution, 0.081 g of hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)-3-phenyl-propyl]undecanoyl]-N-methyl-3(S)-pyridazinecarboxamide (diastereoisomer 1) in the form of a white solid.

nmr (MeOD): 7.28-7.05 (m,5H); 5.09 (m,1H); 4.08-3.88 (m,1H); 3.06-2.96 (m,1H); 2.74 (s,3H); 2.71-2.53 (m,2H); 2.48-2.25 (m,2H); 2.09-2.00 (m,1H); 1.94-1.75 (m,2H); 1.69-1.15 (m,19H); 0.89 (t,3H,J=6);
MS: 489 $(M+H)^+$.

The starting material was prepared as follows:

(i) 3.414 g of 2(S)-hydroxy-4-phenylbutyric acid were dissolved in 100 ml of N,N-dimethylformamide. 1.215 g of anhydrous potassium carbonate and 1.16 ml of benzyl bromide were added and the mixture was heated while stirring for 3 hours. The mixture was cooled and evaporated, and the residue was partitioned between 100 ml of ethyl acetate and 100 ml of water. The ethyl acetate layer was washed with a further 100 ml of water and then dried over anhydrous magnesium sulphate and evaporated. Flash chromatography on silica gel using hexane/ ether (9:1) for the elution give 3.822 g of benzyl 2(S)-hydroxy-4-phenylbutyrate as a colourless oil, Rf (hexane/ether 9:1) 0.55.

(ii) A solution of 31.9 g of benzyl 2(S)-hydroxy-4-phenylbutyrate and 19.1 ml of pyridine in 200 ml of dry dichloromethane was added while stirring and maintaining the reaction temperature at < -5°C to a solution of 29 ml of trifluoromethanesulphonic anhydride in 400 ml of dry dichloromethane. The mixture was stirred at -10°C for a further 2.5 hours. The reaction mixture was diluted with 150 ml of dichloromethane and washed in succession with two 350 ml portions of 1M hydrochloric acid, two 200 ml portions of saturated sodium hydrogen carbonate solution and 200 ml of saturated sodium chloride solution. After drying over anhydrous magnesium sulphate the solvent was evaporated. The residue was dissolved in 400 ml of ether and filtered to remove insoluble impurities. The ether was evaporated to give 39.58 g of benzyl 2(S)-trifluoromethanesulphonyloxy-4-phenylbutyrate in the form of a pale amber oil.

(iii) A suspension of 2.81 g of 60% sodium hydride in 120 ml of dry N,N-dimethylformamide was cooled to 0°C and a solution of 16.77 g of benzyl tert.butyl malonate in 100 ml of dry N,N-dimethylformamide was added. After the initial reaction had subsided the mixture was heated at 60°C for 2 hours and then cooled to 0°C. A solution of 30.15 g of benzyl 2(S)-trifluoromethanesulphonyloxy-4-phenylbutyrate in 75 ml of dry dichloro-

methane was added while maintaining the reaction temperature at < 5°C. After completion of the addition the mixture was stirred at ambient temperature for 18 hours. The solvent was evaporated and the residue was partitioned between 300 ml of ether and 200 ml of water. The ether layer was washed with water and then with saturated sodium chloride solution, dried over anhydrous magnesium sulphate and evaporated. After purification by flash chromatography on silica gel using hexane/ ether (8:1) for the elution there were obtained 27.66 g of 1,2-dibenzyl 1-tert.butyl 4-phenyl-1(RS),1,2(S)-butanetricarboxylate in the form of a pale amber oil; Rf (hexane/ether 8:1) 0.47.

(iv) A solution of 5.08 g of 1,2-dibenzyl 1-tert.butyl 4-phenyl-1(RS),1, 2(S)-butanetricarboxylate in 90 ml of dry N,N-dimethylformamide was cooled to 0°C and 0.435 g of 60% sodium hydride was added. The mixture was stirred at 0°C for 45 minutes under nitrogen and then for a further 4 hours at ambient temperature. The mixture was cooled to 0°C and a solution of 2.64 g of 1-bromonon-2-yne in 10 ml of dry N,N-dimethylformamide was added. The mixture was stirred for 30 minutes at 0°C and then for a further 18 hours at ambient temperature. The solvent was evaporated and the residue was partitioned between 200 ml of ether and 200 ml of 5% citric acid solution. The ether layer was washed with 5% sodium hydrogen carbonate solution and then with saturated sodium chloride solution, dried over anhydrous magnesium sulphate and evaporated. After purification by flash chromatography on silica gel using hexane/ ether (9:1) for the elution there were obtained 4.733 g of 1,2-dibenzyl 1-tert.butyl 1-(non-2-yn-1-yl)-4-phenyl-1(RS),1,2(S)-butanetricarboxylate in the form of a colourless oil; Rf (hexane/ether 2:1) 0.51.

(v) A solution of 5.45 g of 1,2-dibenzyl 1-tert.butyl 1-(non-2-yn-1-yl)-4-phenyl-1(RS),1,2(S)-butanetricarboxylate in 90 ml of methanol was hydrogenated in the presence of 1.12 g of 10% palladium on carbon for 18 hours. The catalyst was filtered off and the solvent was evaporated to give 3.70 g of 1-tert.butoxycarbonyl-1-nonyl-4-phenyl-1(RS),2(S)-butanedicarboxylic acid in the form of a colourless gum.

(vi) A solution of 3.70 g of 1-tert.butoxycarbonyl-1-nonyl-4-phenyl-1(RS),2(S)-butanedicarboxylic acid in 150 ml of toluene containing 1.54 ml of triethylamine was heated under reflux for 4 hours. The solution was cooled

to ambient temperature and evaporated. The residue was dissolved in dichloromethane and washed in succession with three portions of 1M hydrochloric acid, water and saturated sodium chloride solution. The dichloromethane solution was dried over anhydrous magnesium sulphate and evaporated. The residue was purified by flash chromatography on silica gel using 400 ml of hexane/ ether (19:1) and then hexane/ether (9:1) for the elution. 2.05 g of 1-tert.butyl hydrogen 2(R or S)-nonyl-3(S)-(2-phenyleth-1-yl)succinate, isomer 1, were obtained in the form of a colourless oil.

(vii) A solution of 2.284 g of 1-tert.butyl hydrogen 2(R or S)-nonyl-3(S)-(2-phenyleth-1-yl)succinate in 35 ml of dry N,N-dimethylformamide was treated with 0.835 g of anhydrous potassium carbonate and 1.04 ml of allyl bromide. The mixture was heated while stirring for 4 hours at 50°C. The solvent was evaporated and the residue was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with water and saturated sodium chloride solution, dried over anhydrous magnesium sulphate and evaporated. The residue was purified by flash chromatography on silica gel using hexane/ether (7:1) for the elution and there was obtained 1.985 g of 4-allyl 1-tert.butyl 2(R or S)-nonyl-3(S)-(2-phenyleth-1-yl)succinate in the form of a colourless oil; Rf (hexane/ ether 1:1) 0.78.

(viii) A solution of 2.50 g of 4-allyl 1-tert.butyl 2(R or S)-nonyl-3(S)-(2-phenyleth-1-yl)succinate in 50 ml of dichloromethane was treated with 7.7 ml of trifluoroacetic acid. The mixture was stirred for 3 hours and then the solvent was evaporated. There were obtained 2.37 g of 4-allyl hydrogen 2(R or S)-nonyl-3(S)-(2-phenyleth-1-yl)succinate in the form of a pale amber oil.

(ix) In a manner analogous to that described in Example 1(i), from 0.776 g of 4-allyl hydrogen 2(R or S)-nonyl-3(S)-(2-phenyleth-1-yl)succinate and 0.64 g of tert.butyl hexahydro-1-(benzyloxycarbonyl)-3(S)-pyridazinecarboxylate there was obtained 0.792 g of hexahydro-1-(benzyloxycarbonyl)-2(R or S)-[1(S)-(allyloxycarbonyl)-3-phenylpropyl]undecanoyl]-3(S)-pyridazinecarboxylic acid tert.butyl ester in the form of a colourless gum; Rf (hexane/ethyl acetate 3:1) 0.41.

(x) In a manner analogous to that described in Example 7(iii), from 0.76 g of hexahydro-1-(benzyloxycarbonyl)-2-[2(R or S)-[1(S)-(allyloxycarbonyl)-3-

phenylpropyl]undecanoyl]-3(S)-pyridazinecarboxylic acid tert.butyl ester there was obtained 0.539 g of hexahydro-1-(benzyloxycarbonyl)-2-[2(R or S)-[1(S)-(carboxy)-3-phenylpropyl]undecanoyl]-3(S)-pyridazinecarboxylic acid tert.butyl ester in the form of a colourless gum.

(xi) In a manner analogous to that described in Example 1(iii) (second step), from 0.527 g of hexahydro-1-(benzyloxycarbonyl)-2-[2(R or S)-[1(S)-(carboxy)-3-phenylpropyl]undecanoyl]-3(S)-pyridazinecarboxylic acid tert.butyl ester there was obtained 0.558 g of hexahydro-1-(benzyloxycarbonyl)-2-[2(R or S)-[1(S)-(benzyloxycarbamoyl)-3-phenylpropyl]undecanoyl]-3(S)-pyridazinecarboxylic acid tert.butyl ester in the form of a white foam; MS: 756 $(M+H)^+$.

(xii) In a manner analogous to that described in Example 1(iii) (first step), from 0.55 g of hexahydro-1-(benzyloxycarbonyl)-2-[2(R or S)-[1(S)-(benzyloxycarbamoyl)-3-phenylpropyl]undecanoyl]-3(S)-pyridazinecarboxylic acid tert.butyl ester there was obtained 0.51 g of hexahydro-1-(benzyloxycarbonyl)-2-[2(R or S)-[1(S)-(benzyloxycarbamoyl)-3-phenylpropyl]undecanoyl]-3(S)-pyridazine carboxylic acid in the form of a colourless gum.

(xiii) In a manner analogous to that described in Example 1(ii), from 0.25 g of hexahydro-1-(benzyloxycarbonyl)-2-[2(R or S)-[1(S)-(benzyloxycarbamoyl)-3-phenylpropyl]undecanoyl]-3(S)-pyridazine carboxylic acid there was obtained 0.248 g of benzyl hexahydro-2-[2(R or S)-[1(S)-(benzyloxycarbamoyl)-3-phenylpropyl]undecanoyl]-3(S)-(methylcarbamoyl)-1-pyridazinecarboxylate in the form of a colourless gum; Rf (ethyl acetate) 0.59; MS: 713 $(M+H)^+$.

Example 9

In a manner analogous to that described in the first paragraph of Example 1, from 0.251 g of benzyl hexahydro-2-[2(R or S)-[1(S)-(benzyloxycarbamoyl)-3-phenylpropyl]undecanoyl]-3(S)-(N-methoxy-N-methylcarbamoyl)-1-pyridazinecarboxylate there was obtained 0.137 g of hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)-3-phenylpropyl]undecanoyl]-N-methoxy-N-methyl-3(S)-pyridazinecarboxamide in the form of a white solid.

nmr (MeOD): 7.26-7.09 (m,5H); 5.43 (m,1H); 4.09-3.89 (m,1H); 3.80 (s,3H); 3.19 (s,3H); 3.06-2.98 (m,1H); 2.69-2.52 (m,2H); 2.46-2.37 (m,1H); 2.35-2.22 (m,1H); 2.11-2.03 (m,1H); 1.92-1.76 (m,2H); 1.64-1.12 (m,19H); 0.87 (t,3H,J=6);
MS: 510 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 1(ii), from 0.25 g of hexahydro-1-(benzyloxycarbonyl)-2-[2(R or S)-[1(S)-(benzyloxycarbamoyl)-3-phenylpropyl]undecanoyl]-3(S)-pyridazine carboxylic acid and 50 mg of N,O-dimethylhydroxylamine hydrochloride there was obtained 0.251 g of benzyl hexahydro-2-[2(R or S)-[1(S)-(benzyloxycarbamoyl)-3-phenylpropyl]-undecamoyl]-3(S)-(N-methoxy-N-methylcarbamoyl-1-pyridazinecarboxylate in the form of a white solid; Rf (dichloromethane/methanol/acetic acid/water 240:24:3:2) 0.88; MS 743 $(M+H)^+$.

Example 10

In a manner analogous to that described in the first paragraph of Example 1, from 0.57 g of 2-[2(R or S)-[1(S)-(benzyloxycarbamoyl)-3-phenylpropyl]undecanoyl]-1-(benzyloxycarbonyl)-hexahydro-N-(1,2,2,6,6-pentamethyl-4-piperidinyl)-3(S)-pyridazinecarboxamide there was obtained 0.369 g of hexahydro-2-[2(R or S)-1(S)-(hydroxycarbamoyl)-3-phenylpropyl]-undecanoyl]-N-(1,2,2,6,6-pentamethyl-4-piperidinyl)-3(S)-pyridazine-carboxamide in the form of a white solid.
nmr (MeOD): 7.26-7.10 (m,5H); 5.06 (m,1H); 4.33-4.23 (m,1H); 4.05-3.88 (m,1H); 3.07-2.98 (m,1H); 2.83 (s,3H); 2.72-2.52 (m,2H); 2.46-2.20 (m,2H); 2.16-2.00 (m,3H); 1.93-1.68 (m,4H); 1.64-1.15 (m,32H); 0.88 (t,3H,J=6);
MS: 628 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 1(ii), from 0.545 g of hexahydro-1-(benzyloxycarbonyl)-2-[2(R or S)-[1(S)-(benzyloxycarbamoyl)-3-phenylpropyl]undecanoyl]-3(S)-pyridazinecarboxylic acid and 4-amino-1,2,2,6,6-pentamethyl-piperidine there was obtained 0.572 g of 2-[2(R or S)-[1(S)-(benzyloxycarbamoyl)-3-phenylpropyl]undecanoyl]-1-(benzyloxy-carbonyl)-hexahydro-N-(1,2,2,6,6-pentamethyl-4-piperidinyl)-3(S)-

pyridazinecarboxamide in the form of a white solid; Rf (dichloromethane/methanol/acetic acid/water) 240:23:3:2) 0.36; MS: 852 $(M+H)^+$.

Example 11

In a manner analogous to that described in the first paragraph of Example 1, from 0.19 g of benzyl hexahydro-2-[2(R or S)-[1(S)-(benzyloxycarbamoyl)ethyl]undecanoyl]-3(S)-(methylcarbamoyl)-1-pyridazinecarboxylate there was obtained 0.098 g of hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl]-N-methyl-3(S)-pyridazinecarboxamide in the form of a white solid.

nmr (MeOD): 5.11 (m,1H); 4.00-3.83 (m,1H); 3.10-3.01 (m,1H); 2.81-2.66 (m,4H); 2.40-2.24 (m,1H); 2.11-2.02 (m,1H); 1.95-1.84 (m,1H); 1.70-1.12 (m,18H); 1.04 (d,3H,J=7); 0.89 (t,3H,J=6);

MS: 399 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 8(i)-(xiii), from 2(S)-hydroxypropionic acid there was obtained benzyl hexahydro-2-[2(R or S)-[1(S)-(benzyloxycarbamoyl)ethyl]undecanoyl]-3(S)-(methylcarbamoyl)-1-pyridazinecarboxylate in the form of a colourless gum; Rf (ethyl acetate) 0.38; MS: 623 $(M+H)^+$.

Example 12

In a manner analogous to that described in the first paragraph of Example 1, from 0.277 g of benzyl hexahydro-2-[2(R or S)-[1(S)-(benzyloxycarbamoyl)-3-phenylpropyl]nonanoyl]-3(S)-(methylcarbamoyl)-1-pyridazinecarboxylate there was obtained, after purification by flash chromatography on silica gel using dichloromethane/methanol (30:1) for the elution, 0.081 g of hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)-3-phenylpropyl]nonanoyl]-N-methyl-3(S)-pyridazinecarboxamide in the form of a white solid.

nmr (MeOD): 7.26-7.06 (m,5H); 5.07 (m,1H); 4.05-3.87 (m,1H); 3.04-3.95 (m,1H); 2.71 (s,3H); 2.69-2.51 (m,2H); 2.46-2.23 (m,2H); 2.07-1.99 (m,1H); 1.92-1.73 (m,2H); 1.66-1.13 (m,15H; 0.88 (t,3H,J=6);

MS 461 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 8(iv)-(xiii), from 1,2-dibenzyl 1-tert.butyl 4-phenyl-1(RS),1,2(S)-butanetricarboxylate and 1-bromohept-2-yne there was obtained benzyl hexahydro-2-[2(R or S)-[1(S)-(benzyloxycarbonyl)-3-phenylpropyl]nonanoyl]-3(S)-(methylcarbamoyl)-1-pyridazinecarboxylate in the form of a colourless gum; Rf (dichloromethane/methanol/acetic acid/water 240:24:3:2) 0.75; MS: 685 $(M+H)^+$.

Example 13

In a manner analogous to that described in the first paragraph of Example 1, from 0.43 g of benzyl hexahydro-2-[2(R or S)-[1(S)-(benzyloxycarbonyl)ethyl]nonanoyl]-3(S)-(methylcarbamoyl)-1-pyridazinecarboxylate there was obtained, after purification by flash chromatography on silica gel using dichloromethane/methanol (15:1) for the elution, 0.148 g of hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]nonanoyl]-N-methyl-3(S)-pyridazinecarboxamide in the form of a white solid.
nmr (MeOD): 5.11 (m,1H); 4.00-3.85 (m,1H); 3.09-3.01 (m,1H); 2.80-2.70 (m,4H); 2.39-2.26 (m,1H); 2.11-2.02 (m,1H); 1.94-1.84 (m,1H); 1.71-1.14 (m,14H); 1.04 (d,3H,J=7); 0.88 (t,3H,J=6);
MS: 371 $(M+H)^+$.

The starting material was prepared as follows:

(i) In a manner analogous to that described in Example 8(i)-(iii), from 2(S)-hydroxypropionic acid there was obtained 1,2-dibenzyl 1-tert.butyl 1(RS),1,2(S)-propanetricarboxylate in the form of a colourless oil.

(ii) In a manner analogous to that described in Example 8(iv)-(xiii), from 1,2-dibenzyl 1-tert.butyl 1(RS),1,2(S)-propanetricarboxylate and 1-bromohept-2-yne there was obtained benzyl hexahydro-2-[2(R or S)-[1(S)-(benzyloxycarbonyl)ethyl]nonanoyl]-3(S)-(methylcarbamoyl)-1-pyridazinecarboxylate in the form of a colourless gum; Rf (ethyl acetate) 0.29; MS: 595 $(M+H)^+$.

Example 14

In a manner analogous to that described in the first paragraph of Example 1, from 0.277 g of 1-[2(R or S)-[1(S)-(benzyloxycarbamoyl)ethyl]-undecanoyl]piperidine there was obtained 0.144 g of 1-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl]piperidine in the form of a white solid. nmr (MeOD): 3.67 (t,2H,J=5); 3.61 (t,2H,J=5); 3.12 (dt,1H,J=11,4); 2.39-2.29 (m,1H); 1.75-1.46 (m,7H); 1.41-1.09 (m,15H); 1.00 (d,3H,J=7); 0.87 (t,3H,J=6); MS: 341 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 4(i) and Example 8(x) and (xi), from 0.404 g of 4-allyl hydrogen 2(R or S)-nonyl-3(S)-methyl-succinate [prepared in a manner analogous to that described in Example 8(i)-(viii) from 2(S)-hydroxypropionic acid] and 0.19 ml of piperidine there was obtained 0.284 g of 1-(2(R or S)-[1(S)-(benzyloxycarbamoyl)ethyl]-undecanoyl]piperidine in the form of a colourless gum; Rf (ethyl acetate/ hexane 1:1) 0.19; MS: 431 $(M+H)^+$.

Example 15

In a manner analogous to that described in the first paragraph of Example 1, from 0.264 g of 1-[2(R or S)-[1(S)-(benzyloxycarbamoyl)-3-phenylpropyl]undecanoyl]piperidine there was obtained 0.127 g of 1-[2(R or S)-[1(S)-(hydroxycarbamoyl)-3-phenylpropyl]undecanoyl]piperidine in the form of a white solid.
nmr (MeOD): 7.26-7.06 (m,5H); 3.70-3.50 (m,4H); 3.17-3.08 (dt,1H,J=4,10); 2.58-2.49 (m,1H); 2.45-2.30 (m,2H); 1.84-1.04 (m,24H); 0.87 (t,3H,J=6); MS: 431 $(M+H)^+$.

The starting material was prepared as follows:

(i) In a manner analogous to that described in Example 8(vii) and (viii), from 1-tert.butyl hydrogen 2(R or S)-nonyl-3(S)-(2-phenyleth-1-yl)succinate and benzyl bromide there was obtained 4-benzyl hydrogen 2(R or S)-nonyl-3(S)-(2-phenyleth-1-yl)succinate in the form of an oil which slowly crystallized to a white solid on standing; MS: 439 $(M+H)^+$.

(ii) In a manner analogous to that described in Example 4(i), from 0.407 g of 4-benzyl hydrogen 2(R or S)-nonyl-3(S)-(2-phenyleth-1-yl)succinate and 0.13 ml of piperidine there was obtained 0.403 g of 1-[2(R or S)-[1(S)-(benzyloxycarbonyl)-3-phenylpropyl]undecanoyl]piperidine in the form of a colourless gum; Rf (ethyl acetate/hexane 1:2) 0.53; MS: 506 $(M+H)^+$.

(iii) A solution of 0.4 g of 1-[2(R or S)-[1(S)-(benzyloxycarbonyl)-3-phenylpropyl]undecanoyl]piperidine in 15 ml of methanol was hydrogenated in the presence of 0.123 g of 10% palladium on carbon for 3 hours. The catalyst was filtered off and the solvent was evaporated to give 0.326 g of 1-[2(R or S)-[1(S)-(carboxy)-3-phenylpropyl]undecanoyl]piperidine in the form of a colourless gum; MS: 416 $(M+H)^+$.

(iv) In a manner analogous to that described in Example 1(iii) (second step), from 0.307 g of 1-[2(R or S)-[1(S)-(carboxy)-3-phenylpropyl]undecanoyl]piperidine and 0.130 g of O-benzylhydroxylamine there was obtained 0.268 g of 1-[2(R or S)-[1(S)-(benzyloxycarbamoyl)-3-phenylpropyl]undecanoyl]piperidine in the form of a colourless gum; Rf (hexane/ethyl acetate 2:1) 0.25; MS: 521 $(M+H)^+$.

Example 16

In a manner analogous to that described in the first paragraph of Example 1, from 0.584 g of 2-[2(R or S)-[1(S)-(benzyloxycarbamoyl)-3-phenylpropyl]undecanoyl]-1-(benzyloxycarbonyl)-hexahydro-N-(2,2,6,6-tetramethyl-4-piperidinyl)-3(S)-pyridazinecarboxamide there was obtained 0.406 g of hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)-3-phenylpropyl]-undecanoyl]-N-(2,2,6,6-tetramethyl-4-piperidinyl)-3(S)-pyridazine-carboxamide in the form of a white solid.
nmr (MeOD): 7.17-6.97 (m,5H); 4.96 (m,1H); 4.27-4.14 (m,1H); 3.98-3.78 (m,1H); 2.97-2.88 (m,1H); 2.63-2.43 (m,2H); 2.37-2.15 (m,2H); 2.01-1.88 (m,3H); 1.85-1.67 (m,2H); 1.60-1.04 (m,33H); 0.80 (t,3H,J=6);
MS: 614 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 1(ii), from 0.545 g of hexahydro-1-(benzyloxycarbonyl)-2-[2(R or S)-[1(S)-(benzyloxycarbamoyl)-3-phenylpropyl]undecanoyl]-3(S)-pyridazinecarboxylic acid and 0.178 g of 4-amino-2,2,6,6-tetramethylpiperidine there was obtained 0.592 g of 2-[2(R or S)-[1(S)-(benzyloxycarbamoyl)-3-phenylpropyl]undecanoyl]-1-(benzyloxy-carbonyl)-hexahydro-N-(2,2,6,6-tetramethyl-4-piperidinyl)-3(S)-pyridazine-carboxamide in the form of a colourless gum; MS: 839 $(M+H)^+$.

Example 17

In a manner analogous to that described in the first paragraph of Example 1, from 0.326 g of 2-[2(R or S)-[1(S)-(benzyloxycarbamoyl)ethyl]-undecanoyl]-1-(benzyloxycarbonyl)-hexahydro-N-(2,2,6,6-tetramethyl-4-piperidinyl)-3(S)-pyridazinecarboxamide there was obtained 0.202 g of hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl]-N-(2,2,6,6-tetramethyl-4-piperidinyl)-3(S)-pyridazinecarboxamide in the form of a white solid.
nmr (MeOD): 5.08 (m,1H); 4.37-4.24 (m,1H) 4.01-3.84 (m,1H); 3.11-3.02 (m,1H); 2.81-2.70 (m,1H); 2.38-2.24 (m,1H); 2.13-1.78 (m,5H); 1.72-1.13 (m,31H); 1.04 (d,3H,J=7); 0.86 (t,3H,J=6);
MS: 524 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 1(ii), from 0.38 g of hexahydro-1-(benzyloxycarbonyl)-2-[2(R or S)-[1(S)-(benzyloxycarbamoyl)-ethyl]undecanoyl]-3(S)-pyridazinecarboxylic acid and 0.107 g of 4-amino-2,2,6,6-tetramethylpiperidine there was obtained 0.334 g of 2-[2(R or S)-[1(S)-(benzyloxycarbamoyl)ethyl]undecanoyl]-1-(benzyloxycarbonyl)-hexahydro-N-(2,2,6,6-tetramethyl-4-piperidinyl)-3(S)-pyridazinecarboxamide in the form of a colourless gum; MS: 748 $(M+H)^+$.

Example 18

In a manner analogous to that described in the first paragraph of Example 1, from 0.38 g of 1-[2(R or S)-[1(S)-(benzyloxycarbamoyl)-4-phenylbutyl]undecanoyl]piperidine there was obtained 0.233 g of 1-[2(R or S)-

[1(S)-(hydroxycarbamoyl)-4-phenylbutyl]undecanoyl]piperidine in the form of a white solid.
nmr (MeOD): 7.25-7.06 (m,5H); 3.71-3.60 (m,2H); 3.57-3.48 (m,1H); 3.12-3.02 (m,1H); 2.55 (t,2H,J=7); 2.30-2.19 (m,1H); 1.75-1.05 (m,26H); 0.87 (t,3H,J=6);
MS: 445 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 15(i)-(iv), from 1-tert.butyl hydrogen 2(R or S)-nonyl-3(S)-(3-phenylprop-1-yl)succinate there was obtained 1-[2(R or S)-[1(S)-(benzyloxycarbonyl)-4-phenylbutyl]-undecanoyl]piperidine in the form of a colourless gum; Rf (hexane/ethyl acetate 2:1) 0.37; MS: 535 $(M+H)^+$.

Example 19

In a manner analogous to that described in the first paragraph of Example 1, from 0.55g of 4-[2(R or S)-[1(S)-(benzyloxycarbamoyl)-4-phenylbutyl]undecanoyl]morpholine there was obtained 0.172 g of 4-[2(R or S)-[1(S)-(hydroxycarbamoyl)-4-phenylbutyl]undecanoyl]morpholine in the form of a white solid.
nmr (MeOD): 7.26-7.07 (m,5H); 3.73-3.43 (m,8H); 3.08-2.99 (dt,1H,J=10,4); 2.57 (t,2H,J=7); 2.31-2.22 (m,1H); 1.63-1.07 (m,20H); 0.87 (t,3H,J=6);
MS: 447 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 15(i)-(iv), from 1-tert.butyl hydrogen 2(R or S)-nonyl-3(S)-(3-phenylprop-1-yl)succinate and using morpholine in step ii there was obtained 4-[2(R or S)-[1(S)-(benzyloxycarbamoyl)-4-phenylbutyl]undecanoyl]morpholine in the form of a colourless gum; Rf (hexane/ethyl acetate 2:1) 0.15; MS: 537 $(M+H)^+$.

Example 20

A solution of 0.27 g of benzyl hexahydro-2-[2(R)-[1(R or S)-(carboxy)-4-phenylbutyl]nonanoyl]-3(S)-(alpha(S)-methylbenzylcarbamoyl)-1-pyridazinecarboxylate in 4 ml of dry N,N-dimethylformamide was cooled to

0°C while stirring and 0.075 g of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride and 0.05 g of 1-hydroxybenzotriazole were added. The mixture was stirred at 0°C for 15 minutes and then 0.1 g of O-(tert.butyl-dimethylsilyl)hydroxylamine was added. The mixture was left to return to ambient temperature and was then stirred for 5 hours. Then, the solvent was evaporated and the residue was partitioned between ethyl acetate and 5% aqueous sodium hydrogen carbonate solution. The ethyl acetate layer was separated and the aqueous layer was extracted with two further portions of ethyl acetate. The combined ethyl acetate extracts were washed in succession with water, 1.0M hydrochloric acid and saturated sodium chloride solution. After drying over anhydrous magnesium sulphate the solvent was evaporated to give a colourless gum After purification by flash chromatography on silica gel using dichloromethane/methanol (30:1) for the elution and crystallization from ether containing 1% ethyl acetate there was obtained 0.11 g of 1-(benzyloxycarbonyl)-hexahydro-2-[2(R)-[1(R or S)-(hydroxycarbamoyl)-4-phenylbutyl]nonanoyl]-N-(alpha(S)-methylbenzyl)-3(S)-pyridazinecarboxamide in the form of a white solid.
nmr (MeOD): 7.46-7.05 (m,15H); 5.35-5.24 (m,2H); 4.95-4.83 (m, 1H + H20); 4.66-4.59 (m,1H); 4.23-4.12 (m,1H); 3.37-3.22 (m,1H + MeOD); 3.01-2.89 (m,1H); 2.60 (t,2H,J=7); 2.37-2.24 (m,1H); 1.99-1.86 (m,1H); 1.84-1.73 (m,1H); 1.72-0.98 (m,20H); 0.92-0.77 (m,4H);
MS: 699 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 1(ii) and (iii) (first step), from 0.23 g of hexahydro-1-(benzyloxycarbonyl)-2-[2(R)-[1(R or S)-(tert.butoxycarbonyl)-4-phenylbutyl]nonanoyl]-3(S)-pyridazinecarboxylic acid and 0.05 g of alpha(S)-methylbenzylamine there was obtained 0.27 g of benzyl hexahydro-2-[2(R)-[1(R or S)-(carboxy)-4-phenylbutyl]nonanoyl]-3(S)-alpha(S)-methylbenzylcarbamoyl)-1-pyridazinecarboxylate in the form of a colourless gum.

Example 21

In a manner analogous to that described in the first paragraph of Example 1, from 0.3 g of benzyl 1-[2(R or S)-[1(S)-(benzyloxycarbamoyl)-ethyl]undecanoyl]-hexahydro-1-pyridazinecarboxylate there was obtained,

after purification by flash chromatography using dichloromethane/ methanol (20:1) for the elution, 0.06 g of hexahydro-1-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl]pyridazine in the form of a white solid; nmr (MeOD): 3.97-3.86 (m,1H); 3.84-3.52 (m,2H); 2.95-2.79 (m,2H); 2.35-2.21 (m,1H); 1.81-1.12 (m,20H); 1.02 (d,3H,J=7); 0.87 (t,3H,J=6); MS: 342 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 1(i) and Example 8(x) and (xi), from 0.45 g of 4-allyl hydrogen 2(R or S)-nonyl-3(S)-methyl-succinate and 0.409 g of benzyl hexahydro-1-pyridazinecarboxylate there was obtained 0.313 g of benzyl 1-[2(R or S)-[1(S)-(benzyloxycarbamoyl)ethyl]-undecanoyl]-hexahydro-1-pyridazinecarboxylate in the form of a colourless gum; Rf (ethyl acetate) 0.65.

Example 22

In a manner analogous to that described in the first paragraph of Example 1, from 0.095 g of 1-(benzyloxycarbonyl)-hexahydro-2-[2(R)-1(R or S)-(hydroxycarbamoyl)-4-phenylbutyl]nonanoyl]-N-(alpha(S)-methylbenzyl)-3(S)-pyridazinecarboxamide there was obtained 0.073 g of hexahydro-2-[2(R)-[1(R or S)-(hydroxycarbamoyl)-4-phenylbutyl]nonanoyl]-N-(alpha(S)-methylbenzyl)-3(S)-pyridazinecarboxamide in the form of a white solid; nmr (MeOD): 7.34-7.08 (m,10H); 5.10 (m,1H); 4.97 (q,1H,J=7); 3.98-3.80 (m,1H); 2.95-2.86 (m,1H); 2.63-2.50 (m,3H); 2.27-2.13 (m,1H); 2.07-1.99 (m,1H); 1.74-1.06 (m,22H); 0.87 (m,3H); MS: 565 $(M+H)^+$.

Example 23

In a manner analogous to that described in the first paragraph of Example 1, from 0.34 g of N2-[2(R or S)-[1(S)-(benzyloxycarbamoyl)-4-phenylbutyl]undecanoyl]-N1-methyl-L-prolinamide there was obtained 0.214 g of N2-[2(R or S)-[1(S)-(hydroxycarbamoyl)-4-phenylbutyl]undecanoyl]-N1-methyl-L-prolinamide in the form of a white solid;

nmr (MeOD): 7.26-7.08 (m,5H); 4.29-4.23 (m,1H): 3.75-3.60 (m,2H); 2.93-2.84 (m,1H); 2.70 (s,3H); 2.61-2.47 (m,2H); 2.28-2.17 (m,1H); 2.15-2.01 (m,2H); 1.98-1.82 (m,2H); 1.64-1.11 (m,20H); 0.88 (t,3H,J=7);
MS: 488 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 15(ii)-(iv), from 0.452 g of 4-benzyl hydrogen 2(R or S)-nonyl-3(S)-(3-phenylprop-1-yl)succinate, prepared in a manner analogous to that described in Example 15(i), and 0.193 g of S-proline methylamide there was obtained 0.34 g of N2-[2(R or S)-[1(S)-(benzyloxycarbamoyl)-4-phenylbutyl]undecanoyl]-N1-methyl-L-prolinamide in the form of a colourless gum; Rf (ethyl acetate/hexane 2:1) 0.13;
MS: 578 $(M+H)^+$.

Example 24

In a manner analogous to that described in Example 20, from 0.33 g of 3-[2(R or S)-[1(S)-(carboxy)ethyl]undecanoyl]-N,5,5-trimethyl-4(R)-thiazolidinecarboxamide there was obtained 0.166 g of 3-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl-N,5,5-trimethyl-4(R)-thiazolidine-carboxamide in the form of a white solid;
nmr (MeOD): 4.92-4.63 (m,2H); 4.41 and 4.34 (both s, total 1H); 2.95-2.86 and 2.69-2.61 (both m, total 1H); 2.69 and 2.65 (both s, total 3H); 2.35-2.20 (m,1H); 1.51-1.06 (m,22H); 0.98 and 0.85 (both d, total 3H); 0.80 (t,3H,J=6);
MS: 430 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 1(i) and Example 8(x), from 1.408 g of 4-allyl hydrogen 2(R or S)-nonyl-3(S)-methylsuccinate and 1.053 g of 5,5-dimethyl-4(R)-thiazolidinecarboxylic acid methylamide there was obtained 0.68 g of 3-[2(R or S)-[1(S)-(carboxy)ethyl]undecanoyl]-N,5,5-trimethyl-4(R)-thiazolidinecarboxamide in the form of a colourless gum;
MS: 415 $(M+H)^+$.

Example 25

In a manner analogous to that described in the first paragraph of Example 1, from 0.22 g of 3-[2(R or S)-[1(S)-(benzyloxycarbamoyl)ethyl]-undecanoyl]-N,5,5-trimethyl-4(R)-thiazolidinecarboxamide S,S-dioxide there was obtained 0.128 g of 3-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]-undecanoyl]-N,5,5-trimethyl-4(R)-thiazolidinecarboxamide S,S-dioxide in the form of a white solid;
nmr (MeOD): 5.30 and 5.17 (both d, total 1H); 4.78 and 4.75 (both d, total 1H); 4.58 and 4.54 (both s, total 1H); 2.96-2.86 (m,1H); 2.80 and 2.75 (both s, total 3H); 2.43-2.30 (m,1H); 1.57-1.15 (m,22H); 1.04 and 0.91 (both d, total 3H); 0.88 (t,3H,J=6);
MS: 462 $(M+H)^+$.

The starting material was prepared as follows:

(i) In a manner analogous to that described in Example 1(i), from 1.408 g of 4-allyl hydrogen 2(R or S)-nonyl-3(S)-methylsuccinate and 1.053 g of 5,5-dimethyl-4(R)-thiazolidinecarboxylic acid methylamide there were obtained 1.594 g of 3-[2(R or S)-[1(S)-(allyloxycarbonyl)ethyl]undecanoyl]-N,5,5-trimethyl-4(R)-thiazolidinecarboxamide in the form of a colourless gum; Rf (hexane/ethyl acetate 1:2) 0.31;
MS: 455 $(M+H)^+$.

(ii) A solution of 0.417 g of 3-[2(R or S)-[1(S)-(allyloxycarbonyl)ethyl]-undecanoyl]-N,5,5-trimethyl-4(R)-thiazolidinecarboxamide in 20 ml of dichloromethane was cooled to 0°C and 0.4 g of m-chloroperbenzoic acid was added. The mixture was stirred and allowed to return to ambient temperature. After 24 hours the solvent was evaporated and the residue was dissolved in ethyl acetate and washed with portions of saturated sodium carbonate solution until no more unreacted m-chloroperbenzoic acid could be detected in the ethyl acetate layer. The ethyl acetate layer was dried over anhydrous magnesium sulphate and evaporated to give 0.39 g of 3-[2(R or S)-[1(S)-(allyloxycarbonyl)ethyl]undecanoyl]-N,5,5-trimethyl-4(R)-thiazolidine-carboxamide S,S-dioxide in the form of a colourless gum; Rf (hexane/ethyl acetate 1:2) 0.34;
MS: 487 $(M+H)^+$.

(iii) In a manner analogous to that described in Example 7(iii) and Example 1(iii) (second step), from 0.37 g of 3-[2(R or S)-[1(S)-(allyloxy-carbonyl)ethyl]undecanoyl]-N,5,5-trimethyl-4(R)-thiazolidinecarboxamide S,S-dioxide there was obtained 0.227 g of 3-[2(R or S)-[1(S)-(benzyloxy-carbamoyl)ethyl]undecanoyl]-N,5,5-trimethyl-4(R)-thiazolidinecarboxamide S,S-dioxide in the form of a colourless gum; Rf (ethyl acetate/MeOH 20:1) 0.48;
MS: 552 $(M+H)^+$.

Example 26

In a manner analogous to that described in the first paragraph of Example 1, from 0.31 g of 1-(benzyloxycarbonyl)-hexahydro-2-[2(R or S)-[1(S)-(benzyloxycarbamoyl)ethyl]undecanoyl]-N-methoxy-N-methyl-3(S)-pyridazinecarboxamide there was obtained 0.082 g of hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl]-N-methoxy-N-methyl-3(S)-pyridazinecarboxamide in the form of a white solid;
nmr (MeOD): 5.47 (m,1H); 4.01-3.85 (m,1H); 3.81 (s,3H); 3.20 (s,3H); 3.12-3.03 (m,1H); 2.81-2.71 (m,1H); 2.38-2.26 (m,1H); 2.15-2.06 (m,1H); 1.98-1.84 (m,1H); 1.70-1.53 (m,2H); 1.51-1.11 (m,16H); 1.04 (d,3H,J=7); 0.88 (t,3H,J=6);
MS: 429 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 8(ix)-(xiii), from 0.736 g of 4-allyl hydrogen 2(R or S)-nonyl-3(S)-methylsuccinate and 1.137 g of tert. butyl hexahydro-1-(benzyloxycarbonyl)-3(S)-pyridazinecarboxylate there was obtained 0.316 g of 1-(benzyloxycarbonyl)-hexahydro-2-[2(R or S)-[1(S)-(benzyloxycarbamoyl)ethyl]undecanoyl]-N-methoxy-N-methyl-3(S)-pyridazinecarboxamide in the form of a colourless gum; Rf (ethyl acetate/methanol 20:1) 0.58;
MS: 653 $(M+H)^+$.

Example 27

In a manner analogous to that described in the first paragraph of Example 1, from 0.38 g of 1-(benzyloxycarbonyl)-hexahydro-2-[2(R or S)-[1(S)-(benzyloxycarbamoyl)ethyl]undecanoyl]-N,N-dimethyl-3(S)-pyridazine-

carboxamide there was obtained 0.121 g of hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl]-N,N-dimethyl 3(S)-pyridazine-carboxamide in the form of a white solid;
nmr (MeOD): 5.48 (m,1H); 4.00-3.84 (m,1H); 3.13-3.03 (m,4H); 2.92 (s,3H); 2.81-2.71 (m,1H); 2.38-2.25 (m,1H); 2.06-1.84 (m,2H); 1.71-1.53 (m,2H); 1.50-1.12 (m,16H); 1.04 (d,3H,J=7Hz); 0.88 (t,3H,J=6);
MS: 413 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 8(ix)-(xiii) from 0.736 g of 4-allyl hydrogen 2(R or S)-nonyl-3(S)-methylsuccinate and 1.137 g of tert. butyl hexahydro-1-(benzyloxycarbonyl)-3(S)-pyridazinecarboxylate there was obtained 0.383 g of 1-(benzyloxycarbonyl)-hexahydro-2-[2(R or S)-[1(S)-(benzyloxycarbamoyl)ethyl]undecanoyl]-N,N-dimethyl-3(S)-pyridazine-carboxamide in the form of a colourless gum; Rf (ethyl acetate/methanol 20:1) 0.53;
MS: 637 $(M+H)^+$.

Example 28

In a manner analogous to that described in the first paragraph of Example 1, from 0.197 g of 3-(2(R or S)-[1(S)-(benzyloxycarbamoyl)-4-phenylbutyl]undecanoyl]-N-methyl-4(R)-thiazolidinecarboxamide S,S-dioxide there was obtained 0.062 g of 3-[2(R or S)-[1(S)-(hydroxycarbamoyl)-4-phenylbutyl]undecanoyl]-N-methyl-4(R)-thiazolidinecarboxamide S,S-dioxide in the form of a white solid;
nmr (MeOD): 7.25-7.06 (m,5H); 5.31-5.21 (m,1H); 5.15-5.02 (m,1H); 4.59 and 4.38 (both d, total 1H); 3.73-3.59 (m,1H); 3.53-3.37 (m,1H); 2.95-2.84 (m,1H); 2.74 and 2.71 (both s, total 3H); 2.62-2.24 (m,3H); 1.69-1.10 (m,20H); 0.88 (t,3H,J=6);
MS: 538 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 15(ii)-(iv) and Example 25(ii), from 0.452 g of 4-benzyl hydrogen 2(R or S)-nonyl-3(S)-(3-phenylprop-1-yl)succinate, prepared in a manner analogous to that described in Example (i), and 0.193 g of 4(R)-thiazolidinecarboxylic acid

methylamide there was obtained 0.197 g of 3-[2(R or S)-[1(S)-(benzyl-oxycarbamoyl)-4-phenylbutyl]undecanoyl]-N-methyl-4(R)-thiazolidine-carboxamide S,S-dioxide in the form of a colourless gum.

Example 29

In a manner analogous to that described in the first paragraph of Example 1, from 0.206 g of 3-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]undecanoyl]-N-methyl-4(R)-thiazolidinecarboxamide S,S-dioxide there was obtained 0.064 g of 3-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)-ethyl]undecanoyl]-N-methyl-4(R)-thiazolidinecarboxamide S,S-dioxide in the form of a white solid;
nmr (MeOD): 5.37-5.25 (m,1H); 5.23-5.10 (m,1H); 4.61 and 4.25 (both d, total 1H); 3.81-3.32 (m,4H); 3.05-2.69 (m,8H); 1.61-1.42 (m,2H); 1.39-1.15 (m,H); 0.87 (t,3H,J=6);
MS: 574 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 5(i)-(iii) and Example 25(ii), from dibenzyl 3(RS)-tert.butoxycarbonyl 2(R)-nonylsuccinate and 3-bromomethyl-1,5,5-trimethylhydantoin there was obtained 3-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)-ethyl]undecanoyl]-N-methyl-4(R)-thiazolidinecarboxamide S,S-dioxide in the form of a colourless gum.

Example 30

In a manner analogous to that described in the first paragraph of Example 1, from 0.15 g of 1-(benzyloxycarbonyl)-hexahydro-2-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-4-phenylbutyl]nonanoyl]-N,N-dimethyl-3(S)-pyridazinecarboxamide there was obtained 0.077 g of hexahydro 2-[2(R)-[1(R or S)-(hydroxycarbamoyl)-4-phenylbutyl]nonanoyl]-N,N-dimethyl-3(S)-pyri-dazinecarboxamide in the form of a white solid:

nmr (MeOD): 7.25-7.08 (m,5H); 5.37 (m,1H); 4.00-3.83 (m,1H); 3.08 (s,3H); 3.04-2.95 (m,1H); 2.91 (s,3H); 2.64-2.52 (m,3H); 2.28-2.15 (m,1H); 1.99-1.90 (m,1H); 1.78-1.09 (m,19H); 0.86 (t,3H,J=6);
MS: 489 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 1(ii) and (iii) from 0.23 g of hexahydro-1-(benzyloxycarbonyl)-2-[2(R)-[1-(RS)-(tert.-butoxycarbonyl)-4-phenylbutyl]nonanoyl]-3(S)-pyridazinecarboxylic acid there was obtained 0.15 g of 1-(benzyloxycarbonyl)-hexahydro-2-[2(R)-[1(R or S)-[1-(benzyloxycarbamoyl)-4-phenylbutyl]nonanoyl]-N,N-dimethyl-3(S)-pyridazinecarboxamide in the form of a colourless gum.

Example 31

In a manner analogous to that described in the first paragraph of Example 1, from 0.283 g of 4-[1(R or S)-[1(S)-(benzyloxycarbamoyl)-3-phenylpropyl]undecanoyl]morpholine there was obtained 0.207 g of 4-[2(R or S)-[1(S)-(hydroxycarbamoyl)-3-phenylpropyl]undecanoyl]morpholine in the form of a white solid; nmr (MeOD): 7.28-7.21 (m,2H); 7.17-7.09 (m,3H); 3.71-3.54 (m,8H); 3.15-3.06 (m,1H); 2.61-2.51 (m,1H); 2.46-2.31 (m,2H); 1.87-1.74 (m,1H); 1.62-1.49 (m,2H); 1.46-1.36 (m,1H); 1.35-1.10 (m,14H); 0.89 (t,3H,J=6);
MS: 433 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 15(i)-(iv), from 1-tert.butyl hydrogen 2(R or S)-nonyl-3(S)-(2-phenyleth-1-yl)succinate and using morpholine in step (ii) there was obtained 4-[2(R or S)-[1(S)-(benzyloxycarbamoyl)-3-phenylpropyl]undecanoyl]morpholine in the form of a colourless gum; Rf (ethyl acetate/hexane 1:1) 0.3;
MS: 523 $(M+H)^+$.

Example 32

In a manner analogous to that described in the first paragraph of Example 1, from 0.475 g of 4-[2(R or S)-[1(S)-(benzyloxycarbamoyl)ethyl]-

undecanoyl]morpholine there was obtained 0.203 g of 4-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl]morpholine in the form of a white solid;
nmr (MeOD): 3.82-3.59 (m,8H); 3.15-3.06 (m,1H); 2.43-2.32 (m,1H); 1.62-1.50 (m,1H); 1.45-1.12 (m,15H); 1.04 (d,3H,J=7); 0.90 (t,3H,J=6);
MS: 343 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 15(i)-(iv), from 1-tert. butyl hydrogen 2(R or S)-nonyl-3(S)-methylsuccinate and using morpholine in step (ii) there was obtained 4-[2(R or S)-[1(S)-(benzyloxy-carbamoyl)ethyl]undecanoyl]morpholine in the form of a colourless gum; Rf (ethyl acetate/hexane 1:1) 0.29;
MS: 433 $(M+H)^+$.

Example 33

In a manner analogous to that described in the first paragraph of Example 1, from 0.289 g of N2-[2(R or S)-[1(S)-(benzyloxycarbamoyl)-ethyl]undecanoyl]-N1-methyl-L-prolinamide (diastereoisomer 1) there was obtained 0.112 g of N2-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl]-N1-methyl-L-prolinamide(diastereoisomer 1) in the form of a white solid;
nmr (MeOD): 4.53 and 4.36 (both m, total 1H); 3.81-3.45 (m,2H); 2.92 and 2.68 (both m, total 1H); 2.76 and 2.71 (both s, total 3H); 2.42-2.26 (m,1H); 2.22-1.86 (m,4H); 1.58-1.18 (m,16H); 1.03 and 0.95 (both d, total 3H); 0.89 (t,3H,J=6);
MS: 384 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 15(i)-(iv), from 1-tert.butyl hydrogen 2(R or S)-nonyl-3(S)-methylsuccinate and using S-proline methylamide in step (ii) there was obtained N2-(2(R or S)-[1(S)-(benzyloxy-carbamoyl)ethyl]undecanoyl]-N1-methyl-L-prolinamide as a mixture of diastereoisomer 1 and diastereoisomer 2. Flash chromatography of 0.469 g of this mixture on silica gel using ethyl acetate/methanol (20:1) for the elution gave 0.103 g of diastereoisomer 1; Rf (ethyl acetate) 0.2;
MS: 474 $(M+H)^+$.

Example 34

In a manner analogous to that described in the first paragraph of Example 1, from 0.35 g of N2-[2(R or S)-[1(S)-(benzyloxycarbamoyl)ethyl]-undecanoyl]-4(R)-hydroxy-N1-methyl-L-prolinamide (diastereoisomer 1) there was obtained 0.246 g of 4(R)-hydroxy-N2-[2(R or S)-[1(S)-(hydroxy-carbamoyl)ethyl]undecanoyl]-N1-methyl-L-prolinamide(diastereoisomer 1) in the form of a white solid;
nmr (MeOD): 4.55-4.30 (m,2H); 3.75-3.47 (m,2H); 2.85-2.74 (m,1H); 2.70 and 2.63 (both s, total 3H); 2.33-1.89 (m,3H); 1.51-1.08 (m,16H); 0.97 and 0.86 (both d total 3H,J=6); 0.80 (t,3H,J=6)
MS: 400 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 15(i)-(iv), from 1-tert.butyl hydrogen 1(R or S)-nonyl-3(S)-methylsuccinate and using 4(R)-hydroxy-S-prolinemethylamide in step (ii) there was obtained N2-[2(R or S)-[1(S)-(benzyloxycarbamoyl)ethyl]undecanoyl]-4(R)-hydroxy-N1-methyl-L-prolinamide as a mixture of diastereoisomers which were separated by flash chromatography using ethyl acetate/methanol (50:1 increasing to 10:1) for the elution. Diastereoisomer 2 was eluted first; Rf (ethyl acetate) 0.33;
MS: 490 $(M+H)^+$.

Example 35

In a manner analogous to that described in the first paragraph of Example 1, from 0.352 g of 1,2,3,4-tetrahydro-2-[2(R or S)-[1(S)-(benzyloxy-carbamoyl)-4-phenylbutyl]undecanoyl]isoquinoline there was obtained 0.145 g of 1,2,3,4-tetrahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)-4-phenyl-butyl]undecanoyl]isoquinoline in the form of a white solid;
nmr (MeOD); 7.26-6.92 (m,9H); 4.83 (q,1H,J=16); 4.67 (q,1H,J=16); 3.95-3.75 (m,2H); 2.57-2.36 (m,2H); 2.33-2.23 (m,1H); 1.67-0.98 (m,20H); 0.93-0.80 (m,3H);
MS: 542 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 15(i)-(iv) from 1-tert.butyl hydrogen 2(R or S)-nonyl-3(S)-(3-phenylprop-1-yl)succinate there was obtained 1,2,3,4-tetrahydro-2-[2(R or S)-[1(S)-(benzyloxycarbamoyl)-4-phenylbutyl]undecanoyl]isoquinoline in the form of a colourless gum; Rf (hexane/ ethyl acetate 2:1) 0.23;
MS: 583 $(M+H)^+$.

Example 36

In a manner analogous to that described in the first paragraph of Example 1, from 0.58 g of 4-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]undecanoyl]morpholine (diastereoisomer 1) there was obtained 0.275 g of 4-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-undecanoyl]morpholine (diastereoisomer 1) in the form of a white solid;
nmr (MeOD): 3.90-3.83 (m,1H); 3.81-3.42 (m,8H); 3.24-3.12 (m,2H); 2.98-2.89 (m,1H); 2.85 (s,3H); 1.59-1.10 (m,22H); 0.88 (t,3H,J=6);
MS: 483 $(M+H)^+$.

Example 37

In a manner analogous to that described in Example 20, from 0.89 g of 3-[2(R)-[1(R or S)-(carboxy)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)-ethyl]undecanoyl]-N-methyl-4(R)-thiazolidinecarboxamide there was obtained 0.274 g of 3-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]undecanoyl]-N-methyl-4(R)-thiazolidine-carboxamide in the form of a white solid;
nmr (MeOD): 4.96-4.31 (m,3H); 3.65-3.23 (m,3H); 3.05-2.63 (m,9H); 1.53-1.06 (m,22H); 0.83-0.74 (m,3H);
MS: 542 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 5(i) and (ii) and Example 1(i) and (iii) (first step), from dibenzyl 3(RS)-tert.butoxycarbonyl-2(R)-nonylsuccinate and 3-bromomethyl-1,5,5-trimethylhydantoin there was obtained 3-[2(R)-[1(R or S)-(carboxy)-2-(3,4,4-trimethyl-2,5-dioxo-1-

imidazolidinyl)ethyl]undecanoyl]-N-methyl-4(R)-thiazolidinecarboxamide in the form of colourless gum; Rf (ethyl acetate/methanol 10:1) 0.31;
MS: 527 $(M+H)^+$.

Example 38

In a manner analogous to that described in the first paragraph of Example 1, from 0.479 g of N2-[2(R)-[1(S)-(benzyloxycarbamoyl)-4-phenylbutyl]undecanoyl]-4(R)-hydroxy-N1-methyl-L-prolinamide there was obtained 0.199 g of 4(R)-hydroxy-N2-[2(R)-[1(S)-(hydroxycarbamoyl)-4-phenylbutyl]undecanoyl]-N1-methyl-L-prolinamide in the form of a white solid;
nmr (MeOD): 7.24-7.06 (m,5H); 4.51-4.46 (br.s,1H); 4.42 (t,1H,J=8); 3.80-3.69 (m,2H); 2.92-2.82 (m,1H); 2.73 (s,3H); 2.61-2.41 (m,2H); 2.28-2.20 (m,1H); 2.19-2.10 (m,1H); 2.07-1.97 (m,1H); 1.70-1.10 (m,20H); 0.88 (t,3H,J=7);
MS: 504 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 15(i)-(iv), from 1-tert.butyl hydrogen 2(R or S)-nonyl-3(S)-(3-phenylprop-1-yl)-succinate there was obtained N2-[2(R)-[1(S)-(benzyloxycarbamoyl)-4-phenylbutyl]-undecanoyl]-4(R)-hydroxy-N1-methyl-L-prolinamide in the form of a colourless gum: Rf (ethyl acetate) 0.15;
MS: 594 $(M+H)^+$.

Example 39

In a manner analogous to that described in the first paragraph of Example 1, from 0.48 g of 1-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]undecanoyl]-4-phenylpiperazine there was obtained 0.113 g of 1-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]undecanoyl]-4-phenylpiperazine (diastereoisomer 1) in the form of a white solid;

nmr (MeOD): 7.23 (t,2H,J=8); 6.98 (d,2H,J=8); 6.84 (t,1H,J=7); 3.95-3.78 (m,3H); 3.69-3.57 (m,2H); 3.47 (dd,1H,J=14,6); 3.40-3.22 (m,3H); 3.13-2.91 (m,3H); 2.84 (s,3H), 1.58-1.40 (m,3H); 1.36 (s,3H); 1.34 (s,3H); 1.31-1.13 (m,13H); 0.84 (t,3H,J=7);
MS: 558 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 5(i)-(iii), from dibenzyl 3(RS)-tert.butoxycarbonyl-2(R)-nonylsuccinate and 3-bromomethyl-1,5,5-trimethylhydantoin there was obtained 1-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]undecanoyl]-4-phenylpiperazine in the form of a colourless gum; Rf (ethyl acetate/hexane 4:1) 0.53;
MS: 648 $(M+H)^+$.

Example 40

In a manner analogous to that described in the first paragraph of Example 1, from 0.57 g of 8-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]undecanoyl]-1,4-dioxo-8-azaspiro[4,5]decane there was obtained 0.354 g of 8-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-undecanoyl]-1,4-dioxo-8-azaspiro[4,5]decane (diastereoisomer 1) in the form of a white solid;
nmr (MeOD): 4.0 (s,4H); 3.87-3.70 (m,3H); 3.69-3.53 (m,2H); 3.46 (dd,1H,J=14,6); 3.24 (dt,1H,J=10,4); 3.00-2.91 (m,1H); 2.86 (s,3H); 1.91-1.82 (m,1H); 1.78-1.10 (m,25H); 0.90 (t,3H,J=7);
MS: 539 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 5(i)-(iii), from dibenzyl 3(RS)-tert.butoxycarbonyl-2(R)-nonylsuccinate and 3-bromomethyl-1,5,5-trimethylhydantoin there was obtained 8-[2(R)-[1(R or S)-(benzyloxycarbonyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]undecanoyl]-1,4-

dioxo-8-azaspiro[4,5]decane in the form of a colourless gum; Rf (ethyl acetate) 0.22;
MS: 629 $(M+H)^+$.

Example 41

In a manner analogous to that described in the first paragraph of Example 1, from 0.325 g of 1-[2(R or S)-[1(S)-(benzyloxycarbamoyl)ethyl]-undecanoyl]-4-phenylpiperazine there was obtained 0.07 g of 1-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl]-4-phenylpiperazine in the form of a colourless foam;
nmr (MeOD): 7.26 (t,2H,J=7); 7.00 (d,2H,J=8); 6.88 (t,1H,J=7); 3.96-3.78 (m,4H); 3.30-3.07 (m,5H); 2.45-2.24 (m,1H); 1.65-1.51 (m,1H), 1.49-1.15 (m,15H); 1.06 (d,3H,J=7); 0.88 (t,3H,J=7);
MS: 418 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 15(i)-(iv), from 1-tert.butyl hydrogen 2(R or S)-nonyl-3(S)-methylsuccinate and using 1-phenylpiperazine in step (ii) there was obtained 1-[2(R or S)-[1(S)-(benzyloxycarbamoyl)ethyl]undecanoyl]-4-phenylpiperazine in the form of a colourless gum; Rf (ethyl acetate) 0.58;
MS: 508$(M+H)^+$.

The following Examples illustrate pharmaceutical preparations containing the hydroxamic acid derivatives provided by the present invention:

Example A

Tablets containing the following ingredients may be produced in a conventional manner:

Ingredient	Per tablet
Hydroxamic acid derivative	10.0 mg
Lactose	125.0 mg
Corn starch	75.0 mg
Talc	4.0 mg
Magnesium stearate	1.0 mg
Total weight	215.0 mg

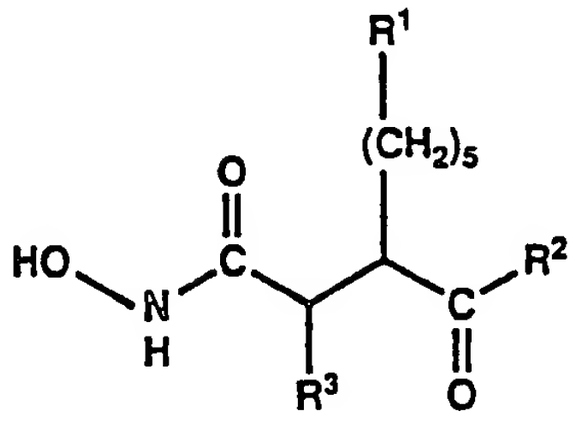
Example B

Capsules containing the following ingredients may be produced in a conventional manner:

Ingredient	Per capsule
Hydroxamic acid derivative	10.0 mg
Lactose	165.0 mg
Corn starch	20.0 mg
Talc	5.0 mg
Capsule fill weight	200.0 mg

Claims

1. Compounds of the general formula



(I)

wherein

R^1 represents 1-7C alkyl;

R^2 represents a saturated 5-, 6- or 7-membered monocyclic or bridged N-heterocyclic ring which is attached via the N atom and which, when it is monocyclic, optionally contains $-NR^4-$, -O-,-S-, -SO- or $-SO_2-$ as a ring member and/or is optionally benz-fused or optionally substituted on one or more C atoms by hydroxy, 1-6C alkyl, 1-6C alkoxy, oxo, ketalized oxo, amino, protected amino, mono(1-6C alkyl)amino, di(1-6C alkyl)amino, (1-6C alkoxy)carbonyl, hydroxymethyl, (1-6C alkoxy)methyl, hydroxyimino, carbamoyl, mono(1-6C alkyl)carbamoyl, di(1-6C alkyl)carbamoyl, N-(1-6C alkyl)-N-(1-6C alkoxy)carbamoyl, aryl-(1-6C alkyl)carbamoyl, 3-6C cycloalkylcarbamoyl, 2,2,6,6-tetra(1-6C alkyl)-4-piperidinylcarbonyl or 1,2,2,6,6-penta(1-6C alkyl)-4-piperidinylcarbonyl;

R^3 represents 1-6C alkyl or a group of the formula $-(CH_2)_m$-aryl or $-(CH_2)_m$-Het in which m stands for 1-4 and Het represents a 5- or 6-membered N-heterocyclic ring which (a) is attached via the nitrogen atom, (b) optionally contains N, O and/or S as additional hetero atom(s), (c) is substituted by oxo on one or both C atoms adjacent to the linking N atom and (d) is optionally benz-fused or optionally substituted on one or more other carbon atoms by 1-6C alkyl or oxo and/or on any additional N atom(s) by 1-6C alkyl or aryl; and

R^4 represents hydrogen, 1-6 alkyl, aryl or a protecting group;

and pharmaceutically acceptable salts thereof.

2. Compounds according to claim 1, wherein R^2 represents a saturated 5-, 6- or 7-membered monocyclic or bridged N-heterocyclic ring which is attached via the N atom and which, when it is monocyclic,

optionally contains -NR^4-, -O-,-S-, -SO- or -SO_2- as a ring member and/or is optionally substituted on one or more C atoms by hydroxy, 1-6C alkyl, 1-6C alkoxy, oxo, ketalized oxo, amino, protected amino, mono(1-6C alkyl)amino, di(1-6C alkyl)amino, (1-6C alkoxy)carbonyl, hydroxymethyl, (1-6C alkoxy)-methyl, hydroxyimino, carbamoyl, mono(1-6C alkyl)carbamoyl, di(1-6C alkyl)carbamoyl, N-(1-6C alkyl)-N-(1-6C alkoxy)carbamoyl, aryl-(1-6C alkyl)carbamoyl, 3-6C cycloalkylcarbamoyl, 2,2,6,6-tetra(1-6C alkyl)-4-piperidinylcarbonyl or 1,2,2,6,6-penta(1-6C alkyl)-4-piperidinylcarbonyl; and R^4 represents hydrogen, 1-6 alkyl or a protecting group.

3. Compounds according to claim 1 or claim 2, wherein R^1 represents ethyl or n-butyl.

4. Compounds according to claim 1, claim 2 or claim 3, wherein R^2 represents a saturated monocyclic N-heterocyclic ring.

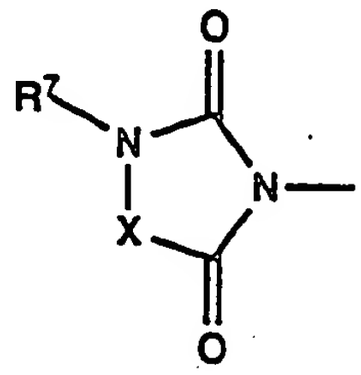
5. Compounds according to claim 4, wherein R^2 represents a 1-pyrrolidino, piperidino, morpholino, thiazolidin-3-yl, piperazino or hexahydro-2-pyrazinyl ring.

6. Compounds according to claim 5, wherein R^2 represents 2-(methylcarbamoyl)-pyrrolidino, 2-(methylcarbamoyl)-4-hydroxy-pyrrolidino, piperidino, 1,2,3,4-tetrahydroisoquinolino, 1,4-dioxa-8-azaspiro[4.5]decan-8-yl, 4-(methylcarbamoyl)-5,5-dimethyl-thiazolidin-3-yl, 4-(methylcarbamoyl)-5,5-dimethyl-thiazolidin-3-yl S,S-dioxide, 4-(methylcarbamoyl)-thiazolidin-3-yl, 4-(methylcarbamoyl)-thiazolidin-3-yl S,S-dioxide, 4-phenylpiperazino, hexahydro-2-pyridazinyl or hexahydro-2-pyridazinyl which is substituted in the 3-position by methylcarbamoyl, cyclohexylcarbamoyl, 2,2,6,6-tetramethyl-4-piperidinylcarbamoyl, 1,2,2,6,6-pentamethyl-4-piperidinylcarbamoyl, N-methyl-N-methoxycarbamoyl, dimethylcarbamoyl or α-methylbenzyl-carbamoyl or in the 3-position by α-methylbenzylcarbamoyl and in the 1-position by benzyloxycarbonyl.

7. Compounds according to any one of claims 1 to 6, wherein R^3 represents methyl or a group of the formula -$(CH_2)_m$-aryl or -$(CH_2)_m$-Het.

8. Compounds according to claim 7, wherein the group of the formula -$(CH_2)_m$-aryl is 2-phenylethyl or 3-phenylpropyl.

9. Compounds according to claim 7, wherein the group of the formula $-(CH_2)_m$-Het has the formula



(c)

wherein R^7 represents hydrogen, lower alkyl or aryl and X represents -CO-, $-CH_2$-, -CH(lower alkyl)-, $-C(\text{lower alkyl})_2$-, -NH-, -N(lower alkyl)- or -O-; or, when R^7 represents lower alkyl and X represents -N(lower alkyl)-, the lower alkyl groups can be joined to form a 5-, 6- or 7-membered ring.

10. Compounds according to claim 9, wherein R^7 represents lower alkyl and X represents $-C(\text{lower alkyl})_2$-.

11. Compounds according to claim 10, wherein R^7 represents methyl and X represents $-C(CH_3)_2$-.

12. A compound according to claim 2 selected from the following:

2-[2(R)-[1(R or S)-(Hydroxycarbamoyl)-4-phenylbutyl]nonanoyl]-hexahydro-N-methyl-3(S)-pyridazinecarboxamide,

N-cyclohexyl-hexahydro-2-[2(R)-[1(RS)-(hydroxycarbamoyl)-4-phenylbutyl]nonanoyl]-3(S)-pyridazinecarboxamide,

hexahydro-2-[2(R)-[1(RS)-(hydroxycarbamoyl)-4-phenylbutyl]-nonanoyl]-N-(2,2,6,6-tetramethyl-4-piperidinyl)-3(S)-pyridazinecarboxamide,

1-[2(R)-[1(R or S)-(hydroxycarbamoyl)-4-phenylbutyl]nonanoyl]-piperidine,

N2-[2(R)-[1(RS)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]nonanoyl]-N1-methyl-L-prolinamide,

1-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]nonanoyl]piperidine,

hexahydro-2-[2(R)-1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]nonanoyl]-N-methyl-3(S)-pyridazine-carboxamide,

hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)-3-phenylpropyl]-undecanoyl]-N-methyl-3(S)-pyridazinecarboxamide,

hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)-3-phenylpropyl]-undecanoyl]-N-methoxy-N-methyl-3(S)-pyridazinecarboxamide,

hexahydro-2-[2(R or S)-(1(S)-(hydroxycarbamoyl)-3-phenylpropyl]-undecanoyl]-N-(1,2,2,6,6-pentamethyl-4-piperidinyl)-3(S)-pyridazine-carboxamide

hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl]-N-methyl-3(S)-pyridazinecarboxamide,

hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)-3-phenylpropyl]-nonanoyl]-N-methyl-3(S)-pyridazinecarboxamide,

hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]nonanoyl]-N-methyl-3(S)-pyridazinecarboxamide,

1-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl]piperidine,

1-[2-(R or S)-[1(S)-(hydroxycarbamoyl)-3-phenylpropyl]undecan-oyl]piperidine,

hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)-3-phenylpropyl]-undecanoyl]-N-(2,2,6,6-tetramethyl-4-piperidinyl)-3(S)-pyridazine carboxamide,

hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl]-N-(2,2,6,6-tetramethyl-4-piperidinyl)-3(S)-pyridazinecarboxamide,

1-[2(R or S)-[1(S)-(hydroxycarbamoyl)-4-phenylbutyl]undecanoyl]-piperidine,

4-[2(R or S)-[1(S)-(hydroxycarbamoyl)-4-phenylbutyl]undecanoyl]-morpholine and

1-(benzyloxycarbonyl)-hexahydro-2-[2(R)-[(R or S)-(hydroxycarbamoyl)-4-phenylbutyl]nonanoyl]-N-(α(S)-methylbenzyl)-3(S)-pyridazinecarboxamide.

13. A compound according to claim 1, selected from:

hexahydro-1-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl]-pyridazine,

hexahydro-2-[2(R)-1(R or S)-(hydroxycarbamoyl)-4-phenylbutyl]-nonanoyl]-N-(alpha(S)-methylbenzyl)-3(S)-pyridazinecarboxamide,

N2-[2(R or S)-[1(S)-(hydroxycarbamoyl)-4-phenylbutyl]undecanoyl]-N1-methyl-L-prolinamide,

3-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl-N,5,5-trimethyl-4(R)-thiazolidinecarboxamide,

3-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl-N,5,5-trimethyl-4(R)-thiazolidinecarboxamide S,S-dioxide,

hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl-N-methoxy-N-methyl-3(S)-pyridazinecarboxamide,

hexahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl-N,N-dimethyl-3(S)-pyridazinecarboxamide,

3-[2(R or S)-[1(S)-(hydroxycarbamoyl)-4-phenylbutyl]undecanoyl]-N-methyl-4(R)-thiazolidinecarboxamide,

3-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]undecanoyl]-N-methyl-4(R)-thiazolidinecarboxamide S,S-dioxide,

hexahydro-2-[2(R)-[1(R or S)-(hydroxycarbamoyl)-4-phenylbutyl]-nonanoyl]-N,N-dimethyl-3(S)-pyridazinecarboxamide,

4-[2(R or S)-[1(S)-(hydroxycarbamoyl)-3-phenylpropyl]undecanoyl]-morpholine,

4-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl]morpholine,

N2-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl]-N1-methyl-L-prolinamide,

4(R)-hydroxy-N2-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl]-N1-methyl-L-prolinamide,

1,2,3,4-tetrahydro-2-[2(R or S)-[1(S)-(hydroxycarbamoyl)-4-phenylbutyl]undecanoyl]isoquinoline,

4-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]undecanoyl]morpholine,

3-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]undecanoyl]-N-methyl-4(R)-thiazolidinecarboxamide,

4(R)-hydroxy-N2-[2(R)-[1(S)-(hydroxycarbamoyl)-4-phenylbutyl]-undecanoyl]-N1-methyl-L-prolinamide,

1-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]undecanoyl]-4-phenylpiperazine,

8-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]undecanoyl]-1,4-dioxo-8-azaspiro[4.5]decane and

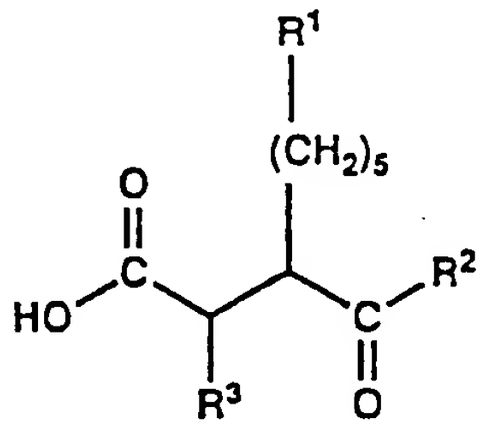
1-[2(R or S)-[1(S)-(hydroxycarbamoyl)ethyl]undecanoyl]-4-phenyl-piperazine.

14. Compounds according to any one of claims 1-13 for use as therapeutically active substances.

15. Compounds according to any one of claims 1-13 for use in the control or prevention of degenerative joint diseases or in the treatment of invasive tumours, atherosclerosis or multiple sclerosis.

16. A process for the manufacture of the compounds claimed in any one of claims 1-13, which process comprises

(a) reacting an acid of the general formula



(II)

wherein R^1, R^2 and R^3 have the significance given in claim 1, with a compound of the general formula

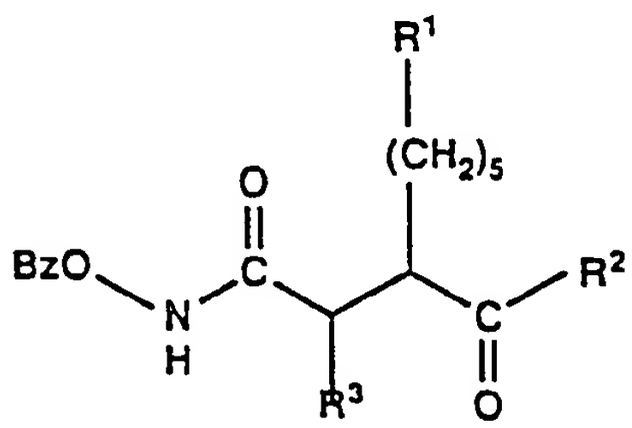
$$H_2N\text{-}OZ \qquad \text{(III)}$$

wherein Z represents hydrogen, tri(lower alkyl)silyl or diphenyl(lower alkyl)silyl,

and, where required, cleaving off any diphenyl(lower alkyl)silyl group present in the reaction product,

or

(b) catalytically hydrogenating a compound of the general formula



(IV)

wherein R^1, R^2 and R^3 have the significance given in claim 1 and Bz represents benzyl,

and,

if desired, converting a compound of formula I obtained into a pharmaceutically acceptable salt.

17. Compounds of formulae II and IV given in claim 16.

18. A medicament containing a compound according to any one of claims 1-13 and a therapeutically inert carrier material.

19. A medicament for the control or prevention of degenerative joint diseases or for the treatment of invasive tumours, atherosclerosis or multiple sclerosis, containing a compound according to any one of claims 1-13 and a therapeutically inert carrier material.

20. A process for the manufacture of medicaments, especially for use in the control or prevention of degenerative joint diseases or in the treatment of invasive tumours, atherosclerosis or multiple sclerosis, which process comprises bringing a compound according to any one of claims 1-13 with a therapeutically inert carrier material and bringing the mixture into a galenical administration form.

21. The use of a compound according to any one of claims 1-13 in the control or prevention of illnesses, especially for the control or prevention of degenerative joint diseases or for the treatment of invasive tumours, atherosclerosis or multiple sclerosis.

22. The use of a compound according to any one of claims 1-13 for the manufacture of a medicament for the control or prevention of degenerative joint diseases or for the treatment of invasive tumours, atherosclerosis or multiple sclerosis.

23. Compounds according to any one of claims 1-13, whenever prepared according to a process according to claim 16.

24. The compounds, intermediates, processes, formulations and uses as hereinbefore described.

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INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/EP 95/01956

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D237/04 A61K31/50 C07D401/04 C07D211/16 A61K31/445
C07D403/06 C07D401/06 C07D265/30 A61K31/535 C07D275/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A A	JP,A,07 002 797 (SANKYO) 6 January 1995 see column 6 & DATABASE WPI Week 9511 Derwent Publications Ltd., London, GB; AN 78001 see abstract	1-24
P,A	EP,A,0 606 046 (CIBA-GEIGY AG) 13 July 1994 see claim 1	1-24
A	EP.A,0 575 844 (F.HOFFMANN-LA ROCHE AG) 29 December 1993 see claim 1	1-24

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 September 1995	-3. 10. 95
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer Gettins, M

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INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/EP 95/01956

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO,A,93 09097 (SANKYO) 13 May 1993 see page 9 - page 15; claim 1	1-24
P,A	& EP,A,0 621 270 (SANKYO) 26 October 1994 see page 7 - page 11	1-24
A	WO,A,92 09556 (GALARDY) 11 June 1992 see claim 1	1-24

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		NO-A-	940038	07-07-94
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Form PCT/ISA/210 (patent family annex) (July 1992)

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Information on patent family members

In: ional Application No
PCT/EP 95/01956

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		CA-A-	2096221	22-05-92
		EP-A-	0558635	08-09-93
		EP-A-	0558648	08-09-93
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		WO-A-	9209563	11-06-92
		US-A-	5239078	24-08-93
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